Novel prognostic biometrics in computed tomography in patients with abdominal aortic aneurysm

Buijs, Ruben Victor Cornelis

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Ruben V.C. Buijs

The printing of this thesis was financially supported by:

Chipsoft – www.chipsoft.nl

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Sectra – www.sectra.com

Ruben V.C. Buijs
"Novel prognostic biometrics in computed tomography in patients with abdominal aortic aneurysm"
PhD thesis, University Medical Center Groningen, with a summary in Dutch

ISBN 978-94-6380-016-7 (printed version)
ISBN 978-94-034-1088-3 (electronic version)

Cover illustration Robert L. Kiss // Instagram: @robertlkiss & @robertlkissart
Lay-out & cover design by Marloes Buijs
Printed by: ProefschriftMaken || www.proefschriftmaken.nl

rijksuniversiteit groningen

Novel prognostic biometrics in computed tomography in patients with abdominal aortic aneurysm

Proefschrift

ter verkrijging van de graad van doctor aan de

Rijksuniversiteit Groningen

op gezag van de

rector magnificus prof. dr. E. Sterken

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 17 oktober 2018 om 16:15 uur

door

Ruben Victor Cornelis Buijs

geboren op 8 juli 1989

te Amstelveen

Promotor:	Prof. dr. C.J. Zeebregts
Copromotores:	Dr. T.P. Willems Dr. I.F.J. Tielliu
Beoordelingscommissie:	Prof. dr. R. Balm Prof. dr. J.L. Hillebrands Prof. dr. T. Leiner
Paranimfen:	C.C. Docter M.R. Bongaards

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Chapter 1

General introduction

GENERAL INTRODUCTION

The abdominal aorta is considered aneurysmal once it exceeds 3.0 cm in diameter. Current estimations of abdominal aortic aneurysm (AAA) prevalence are between 1.3% to 12.5% for men, and 0 to 5.2% for women[1], with a most recent estimation of 1.4% in the American population[2]. The annual rupture risk of abdominal aortic aneurysms (AAA) is currently estimated at 5.3% diameters ranging from 5.5 to 7.0 cm and 6.3% diameters over 7.0 cm. Since 2000, AAA rupture related mortality has been on the decline. This decline seems to be highly correlated to the decrease in tobacco consumption, especially considering the slower decline or stagnation of AAA rupture in countries with higher tobacco use[2]. Despite a relatively low incidence, the all-cause, in-hospital mortality of acute AAA rupture, for both treated and untreated patients, is reported to be 53.1% in the United States and 65.9% in the United Kingdom. Mortality rates after surgery are comparable in the United States and the United Kingdom, ranging respectively between 41.65 and 41.77% [3]. The risks of aneurysmal growth depend on the size of the aneurysm, with a strong positive correlation between aortic diameter increase and AAA rupture. Thus, a yearly increase of 1.0 cm was decided a clinical indication for elective surgery. Treatment criteria are dependent on the type of aneurysm and differ slightly between men and women. Generally, a fusiform aneurysm is recommended to be repaired as it grows to over 5.5 cm. As there are fewer data on saccular aneurysm rupture risk, no definitive diameter criteria have been decided. For women in particular, AAA is less likely to develop, yet are prone to rupture at smaller diameters. Thus, surgical treatment is suggested for women with AAA diameters of 5.0 to 5.4[2] Once the aortic diameter either reaches 5.0 cm for women or 5.5 cm for men, the risk of rupture becomes greater than the operative risk. This diameter criterion is considered the most important risk factor for abdominal aortic aneurysm (AAA) rupture[1]. Regrettably, there is very little data on rupture rates for patients with small aneurysms (30-55 mm diameter). One systematic review by Powell et al. did provide some insight, despite heavily heterogeneous included studies. Their estimations lie between 0 and 1.61 ruptures per 100 person-years [4,5]. Further, anecdotal, evidence from experiences in the University Medical Center Groningen imply that the diameter criterion is not fully predictive for the incidence and outcomes of AAA rupture. Also, as preventive surgical interventions are not free of morbidity

and mortality, it is recommended to further distinguish between low- and high-risk patients. Thus, additional predictive factors should be detected to expand the current knowledge on which patients are more prone to AAA rupture.

Other potential rupture risk predictors have already been identified, such as female gender, family history of AAA, hypertension, chronic obstructive pulmonary disease (COPD) and tobacco abuse [2,6,7]. Additional covariates in the prediction of AAA rupture rate, such as these, will be further discussed in chapter 2. Despite extensive research, no clinically relevant factors have been found to aid the prediction of AAA rupture. Abdominal aortic calcification has also been proposed as a predictive factor for AAA rupture risk. Calcification of the coronary arteries has repeatedly connected cardiovascular events to the degree of calcification, both through positive correlation[8-10] and negative[11]. There is some overlap in the pathophysiological basis for the development of both obstructing coronary disease and dilating aortic diseases, especially with regard to vascular calcification. Also, despite the strong pathophysiological correlation between inflammation and calcification, which will be elucidated below, a recent publication by Blomberg et al. suggest that vascular calcification and inflammation, at least for the thoracic aorta, may have separate effects on cardiovascular disease (CVD) risk. Their results insinuate that calcification is not merely a proxy of extensive vascular inflammation, but also a risk factor in its own right[12]. Therefore, it is hypothesized that aortic calcification could play a role in the prediction of AAA rupture.

Pathogenesis

Aneurysmal dilation of the aorta is either specified by an underlying disease or unspecific. The chronic process of atherosclerosis has been found in either group. Specific causes of AAA are connective tissue disorders like Marfan's disease or vascular type Ehlers-Danlos disease, acute or chronic infection, inflammatory vessel diseases such as penetrating atherosclerotic ulcers, and direct physical trauma. These causes collectively contribute to a small portion of AAA patients, as most are a consequence of unspecific degeneration over an extended period of time. A hereditary component has also been identified, although no specific genetic cause has been found [1]. Most often, AAA development is unspecific and follows a general cascade of degeneration, such as in atherosclerosis, potentially leading to rupture. The abdominal aortic structural

integrity is mainly provided by rich connective tissue of interwoven fibrin, elastin and collagen in the medial and adventitial wall, as well as the smooth muscle cell (SMC) layer in the medial wall. In aneurysmal development, the elasticity and rigidity of the aorta is compromised as elastin and collagen fibers decrease in number and in size, both due to fragmentation of the fibers and an imbalance in synthesis and degradation. Degradation of elastin and collagen develops through upregulation of matrix metalloproteinases (MMP) and an imbalance of their inhibitory counterparts, the tissue inhibitor metalloproteinases (TIMP). In part, extracellular matrix proteins and (inhibitory) proteases are expressed by SMCs, thereby initiating protective remodeling of the aortic wall. Activation of SMCs requires increased oxygenation, which can be hampered both by thickening of the medial wall and mural thrombus formation. As such, increased medial neovascularization is required to maintain adequate microcirculation of the afflicted section of the aortic wall. As the degradation of the aortic wall continues, the diameter of the wall increases up to a point where the blood pressure exerts a force greater than the tensile strength at the weakest area of the aneurysm, leading to rupture. Several components of atherosclerotic disease may overlap and interact with aneurysmal development, yet there are distinct differences between them. For instance, contrary to systemic atherosclerosis, some tissue protease inhibitors such as TIMP-2 are expressed at a lower rate in aneurysmal disease. Also, in the absence of atherosclerotic disease, aortic aneurysms can still develop, although at a far lower rate [13].

Aneurysmal calcifications are theorized to be a defense mechanism to shield an atherosclerotic plaque, or otherwise weakened vascular wall, from the mechanical and biochemical effects exerted by passing blood. Although little is known about why vascular calcification happens, much has been discovered about its pathophysiology. Generally, vascular calcification affects the intimal wall and is a consequence of atherosclerotic disease. In far fewer cases, it follows metabolic, electrolyte, or pH imbalances in, for example, end-stage renal disease. Moreover, the pathogenesis of medial calcification and atherosclerotic calcification differ as well. Only the pathogenesis of atherosclerotic calcification will be outlined here, since it is most likely to be correlated with AAA. The process of vascular calcification is not yet fully understood, but theoretically these are separated along two distinct pathways, active and passive. The active pathway

constitutes a cascade of the cellular and molecular changes of blood vessels to damage, such as atherosclerotic disease, changing the form and function of the cells to protect the local environment from further harm. The passive pathway theorizes that serum calcium and phosphate ions can precipitate and dissolve on the vascular lumen surface at different rates, depending on the reactive capabilities of the cellular components of the vessel wall. This, in time, could aggregate to vascular calcifications. The active and passive pathways may not be mutually exclusive and even act in parallel. Although the passive pathway has mainly been shown to impact medial calcification, it cannot be entirely separated from atherosclerotic vascular damage. The active pathway originates from exposure of a damaging factor, such as chronic inflammation found in aneurysm development and atherosclerosis. Local lipid oxidation and expression of inflammatory cytokines and cells lead to up-regulation of osteogenic regulatory gene expression in vascular smooth muscle cells. Vascular smooth muscle cells are capable of de-differentiation towards osteogenesis by expressing bone matrix proteins that either promote osteoblast formation or depress osteoclast formation. The details of these processes can be found elsewhere. [14, 15]

Diagnostic options

Patients with symptomatic AAA are most often discovered as patients presenting with symptoms such as lower back pain of flank pain, and a palpable, pulsatile abdominal aortic swelling. Under critical circumstances CT angiography will be applied primarily for the most effective imaging, while ultrasound is most practical and also highly effective in the follow-up of AAA patients with aneurysms under 5.5 cm diameter. Most AAA tend to develop unnoticed, which is exemplified by the significant incidental findings of AAA in patients with a low a priori risk for aneurysmal disease. Between 24.8 and 52% of AAA cases are found by abdominal x-ray, CT (angiography), duplex ultrasound, and magnetic resonance (MR) imaging applied for other reasons or during non-related abdominal surgery [16]. In a study by Van Walraven et al., these incidental AAA patients had aortic diameters of 40.0 ± 10.6 mm (mean ± SD), and thus were not eligible for elective treatment in most of the cases. Over the years, all of these modalities have only shown to provide increasingly accurate diameter measurements of the aorta, yet have not improved on further distinguishing between low- and high-risk patients [17]. Positron-emission tomography and bio-optical imaging have great potential, yet are

still in early stages of experimental research and cannot be implemented in clinical settings as easily as CT and CT angiography modalities. Finally, and most importantly for this thesis, there is the field of computational analysis. As no additional exposure to radiologic sources is required, post-hoc analysis of already performed clinical scans offers a multitude of possibilities to strengthen existing modalities and allows for the safe and low-cost exploration of novel imaging assessment techniques.

Vascular calcification is easily recognizable on radiographic images and has therefore been of interest in cardiovascular imaging from early on. For an extended time, vascular calcification was the only cardiac entity that was visualized easily on radiographic images. As cardiovascular calcification was associated with disease, it garnered increased attention, especially as radiology became more accurate and introduced contrast-enhanced imaging. Agatston et al. were the first to provide a semi-quantitative analysis of vascular calcification by imaging the coronary arteries. The coronary artery calcification (CAC) score was developed, grouping the degree of CAC by their signal intensity, provided in Hounsfield Units (HU). Five categories were distinguished, separating non-calcified structures of lower than 130 HU from the three calcification classes of 130 -199 HU, 200-299, 300-399 and >400. With this tool, the authors showed that, as the CAC increased, the risk of coronary artery disease increased [18]. It is supposed that the radiological presence of calcification in the coronary vessels visualizes the narrowing of the vessel, which could potentially lead to obstruction and subsequent infarction. Additionally, since calcification is connected to atherosclerotic plaque stability and vascular inflammation, this correlation was also found in biomechanical CT studies [19]. However, the connection between clinical calcification scores and vascular health has shown controversial results in positron emission CT studies, depending on the tracer that was applied [20-22]. Extrapolation to other vessels was readily done, as seen in carotid arteries [23], intracerebral arteries [24], the aortic arch [25] and the abdominal aorta followed in kind. A vast amount of studies have been published on the role of AAA calcification scores on CT scans and their use in assessing a host of different clinical outcomes. These included studies on non-alcoholic fatty liver disease, colorectal anastomotic leakage and renal disease [26-28]. Nonetheless, little has been published on the technical aspects and issues of measuring AAA calcification on CT, and fewer still on abdominal aortic calcification and its

relation to AAA rupture. Current developments in this field will be discussed further in this dissertation.

Treatment

As outlined before, there is a significant number of non-symptomatic AAA patients that present incidentally, without symptoms, as a consequence of a diagnostic work-up for unrelated diseases. The general advice for lowering cardiovascular risk is also followed for cases with AAA. Cessation of smoking, maintaining a healthy diet and physical condition are all part of the global consensus for the risk reduction of aortic disease [1, 2]. In Holland, this is supplemented with statins, anti-platelet and anti-hypertensive drugs [29-32]. There is an increasing body of evidence suggesting that small aneurysms between 30-49 mm have a decreased rate of growth when treated with beta-blockers. Some contradictory evidence has been presented, thus no recent consensus has been reached with regard to the role of beta-blockers in the management of small aneurysms [1, 2, 33]. The main recommendation, however, is yearly or biyearly clinical follow-up through imaging, either by ultrasound or CT [1].

As aneurysms tend to grow, most patients are recommended to undergo surgical treatment once the threshold of 5.0-5.5 cm diameter is reached. This is performed electively either through open or endovascular aortic repair (EVAR). As of yet, neither of these methods has been proven to outperform one another in terms of overall mortality and morbidity rates, especially at the longer term. EVAR treatments tend to result in reduced (retroperitoneal) blood loss, reduced cardio-pulmonary morbidity and mortality, reduced duration of the repair and improved long-term outcomes for female patients especially. With regard to 30-day mortality and in-hospital re-intervention rates, EVAR is on par with open repair of AAA. However, EVAR treated patients require long-term re-interventions to a greater extent than open repair (odds ratio 2.08; P=0.003) [34].

Adverse circumstances for EVAR are mainly dictated by anatomical characteristics of the abdominal aorta. These are: 1. aneurysm size; 2. aneurysm location (supra-, juxta- or infrarenal); 3. aortic neck length; 4. tapering of the neck; 5. presence of calcification or thrombus; 6. angulation and 7. tapering of the neck [35, 36]. An aortic neck

is considered "hostile" as more of these characteristics are found in one patient. These have ramifications for the incidence of endoleak [37]. Endoleak is defined as leakage of blood into the aneurysmal sack that was bypassed by the endoprosthesis. Five types have been identified [1]. Type 1 is defined as the leakage of blood into the aneurysm sack through the proximal or distal attachment sites of the endograft. Leakage at the proximal end of the prosthesis is defined as endoleak type 1A, whereas endoleak type 1B occurs at the distal end. Endoleak type 1A in particular is likely to be influenced by pre-operative factors such as aneurysm neck sizing and endograft selection, especially with regard to more or less hostile neck characteristics [36]. There are few publications that provide evidence on the optimal sizing methods, so clinicians need to rely on variable instructions by different endograft producers combined with local knowledge and personal experience for the selection of the right endograft sizes. Therefore, this field leaves ample room for further scientific research.

Endovascular aortic sealing has been proposed as an alternative approach to aortic repair in the presence of hostile aortic neck characteristics. Instead of solely placing aortic prostheses inside the dilated aortic lumen, the entire aneurysm is occupied by endobags that are gradually filled by a solidifying biocompatible polymer. Studies have already found low proximal endoleak type 1 incidences [38], a decreased incidence of endoleak type 2 [39, 40] and improvement in ease of use, especially with regard to pre-operative sizing under acute circumstances [41].

Aims and outline of the thesis

This thesis investigates several novel developments in the field of CT biometry for the purpose of improving treatment, diagnostics and post-operative outcomes for abdominal aortic aneurysm patients. First, to place this thesis in the current clinical and temporal context, chapter 2 outlines the spectrum of relevant modalities that are applied in the imaging of abdominal aortic aneurysm in part 1. It also provides a background on the most promising experimental options for rupture risk assessment, especially with regard to aortic calcification, as outlined in part 2. Building on this theoretical basis, chapter 3 continues on how aortic calcification can be measured on CT images. Part 1 of this chapter applies the Abdominal Aortic Calcification-8 (AAC-8) scoring tool, a relatively crude method of calcification analysis, to establish

the clinical relevance of aortic calcification measurements. Following the outcomes of this paper, the aim was to replace AAC-8 scoring tool by a more accurate tool, a fully quantitative computational analysis tool for exact measurement of aortic calcification mass and volume. To this end, the reliability of this tool was tested under clinically relevant circumstances in part 2. This was performed by assessing the effects of CT scanning parameters and the effects of iodine contrast on the measurements of aortic calcification. Regrettably, the reliability of fully quantitative calcification scoring tools on CT was considered highly doubtful as a result of this paper. Especially since aortic neck calcification also plays a significant role in the pre-operative stage of surgical AAA repair. Nonetheless, it would be futile to delve further into clinical calcification scoring in the absence of well-studied and reliable calcification scoring tools. Thus, the focus was shifted to other clinical applications of CT biometry analysis in chapter 4. Part 1 leads with a discussion on one important post-operative complication of EVAR, namely endoleak type 1A. It also contrasts EVAR to the recent application of EVAS treatment, partly as a means of decreasing the risk of endoleak type 1A. Another perspective on endoleak type 1A risk reduction is displayed in part 2 and part 3, through the improvement of the traditional method of endograft sizing using CT biometry. Part 2 provides a mathematical analysis of a novel approach to endograft sizing on CT images. This novel technique focuses on the circumference of the aortic neck, as opposed by the traditional method of endograft sizing, which is based on the diameter of the aortic neck. By comparing their outcomes in a clinical, retrospective, case-control cohort, the traditional method is challenged by the circumference-based method in part 3. Finally, Chapter 5 summarizes this thesis in the general discussion, in which the results of these chapters and their clinical implications are discussed. The discussion expands on several unchallenged paradigms in the field of aortic CT biometry and how this thesis contrasts their assumed validity.

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Chapter 2

Abdominal aortic aneurysm rupture risk and calcification; reviews

2.1

Current state of experimental imaging modalities for risk assessment of abdominal aortic aneurysm

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(Journal of Vascular Surgery 2013;57:851-9)

ABSTRACT

Background: Abdominal aortic aneurysm (AAA) is a major cause of death in developed countries. Patients often lack clinical symptoms, most acute AAA patients do not survive rupture, and subsequent surgical repair has a significant postoperative mortality. Diagnostics for AAAs are currently centered on aneurysm diameter, but recent studies claim this method to be insufficiently accurate. More accurate diagnostic criteria need to be indentified to minimize the amount of unnecessary interventions and to provide earlier diagnosis of rupture-prone AAAs.

Methods: A literature study using the MEDLINE database followed by manual cross-referencing provided original studies concerning AAA diagnostics.

Results: The currently validated imaging modalities such as ultrasound, computed tomography, and magnetic resonance imaging allow AAA research to develop in several directions. Some studies investigate whether clinically visible entities like thrombus, calcification, and vascular anatomy could be implemented directly into clinical practice through use of ultrasound or computed tomography. Experimental studies on wwww ultrasound, positron emission tomography- computed tomography, ultrasound particle image velocimetry and superparamagnetic particles in magnetic resonance imaging propose new methodologies to benefit AAA research. Other studies focus on available technology toward inflammation, metabolism, and the effects of hemodynamics on vascular integrity.

Conclusions: Contradictory outcomes, low availability of experimental imaging modalities, and an often small population size hamper research in this field. Introducing new techniques and biomarkers in current or experimental modalities may prove to be the next step in the development of new diagnostic criteria for the risk assessment of AAA rupture. Until then, the AAA diameter remains the gold standard as a clinical risk factor.

INTRODUCTION

Abdominal aortic aneurysm (AAA) currently is a significant cause of sudden death in developed countries. Its incidence quickly follows atherosclerosis and hypertension in cardiovascular mortality with yearly over 15,000 AAA related deaths in the United States and 8,000 deaths in the United Kingdom. AAA rupture has a mortality rate of 65-85% and only 50% of acute patients reaching the hospital will survive surgery [1]. Since an AAA most frequently occurs in the formerly or currently smoking elder population, it is suspected that its incidence will increase rapidly. AAA treatment now consists of endovascular aneurysm repair (EVAR) or open repair. EVAR shows promising results in reducing aneurysm-related mortality, but the debate remains on its advantages over open repair as no long-term follow-up studies have been able to determine which treatment modality is best [2].

Up to now, measurement of aneurysm diameter is the clinically approved tool for the diagnosis and follow-up of AAA. Small aneurysms (diameter <5.5 cm in men, <5.0 cm in women) are followed up by routine monitoring of growth. Should the aneurysm grow more than one cm/year or over 5.5 cm (men; 5.0 cm in women), surgical intervention is indicated. The results of these population-based studies, however, are just partly helpful when extrapolated to the individual level. Recent studies suggested this method of diameter assessment only is insufficient [3-4]. Subjects with aneurysm diameters well under 5.0 cm can also rupture, whilst up to 25% of aneurysms over 5.5 cm diameter may have very well remained intact until death from other causes [5]. In the search for new diagnostic methods, many different approaches have been explored but have yet to be validated. This review assesses current options and promising new imaging possibilities in AAA rupture risk diagnostics.

MATERIALS AND METHODS

Both the UpToDate and MEDLINE/PubMed databases were searched for the following terms: “abdominal aortic aneurysm” and “AAA” as heading and “diagnosis”, “computed tomography”, “CT”, “ultrasound”, “Doppler”, “magnetic resonance”, “MR”, “imaging”, “angiography”, “PET”, “PET-CT” or “rupture” as keywords.

Further manual cross referencing provided the remaining literature needed. No limitations were set for either languages or time periods.

Clinical risk assessment

AAA remains quiescent in most of the cases. Eventually, AAA rupture classically presents with lower back pain, tenderness of the abdomen and a pulsating abdominal mass that is painful on palpation. A hypovolemic shock can eventually occur. Though a less common entity, symptomatic non-ruptured AAAs present with one or more previously stated symptoms without any form of rupture. Often asymptomatic patients are diagnosed incidentally after receiving ultrasound (US), computed tomography, or magnetic resonance imaging (MRI) for other indications. A few clinically available patient characteristics are known as significant risk factors. A history of smoking and the amount of cigarettes consumed are directly dose- and time period-dependent factors to the development of an AAA [6]. Age, male sex and a positive family history for AAA also increases the risk for developing an AAA [1].

Imaging modalities

Ultrasound-based techniques

US is currently the gold standard in monitoring growth in aneurysms. Being relatively inexpensive, easy to use with low inter-observer variability and no radiation burden, US is considered the perfect AAA screening modality.

In a retrospective cohort study, Lindholt et al. provided new insights in the effects of calcification on AAA development. Through the application of US, the authors found significantly slower expansion rates (Wilcoxon rank sum; $P < .001$) of AAAs in men with small aneurysms (<30 mm) containing calcification in more than 50% of the total AAA wall circumference in comparison to men with calcification in less than 50% of the wall circumference. In spite of these findings, mortality was similar in both groups (hazard ratio: 0.89; $P = .604$). AAA-related hospital admissions were only significantly lower in >50% calcified AAA walls with univariate analysis and not as an independent risk factor for hospital admission when tested in a multivariate model. So whilst it is not protective against AAA symptoms and death, this study suggests calcification might be protective against aneurysm expansion [7]. Some researchers specifically utilize the duplex and Doppler modality of US. Whilst duplex research is

mainly focusing on discovering post-surgical endoleaks and monitoring AAA growth [8], Long et al. discovered new insights in pre-surgical risk assessment using Doppler. They studied 56 patients using tissue Doppler imaging (TDI) aiming to evaluate AAA behavior at different levels of compliance and diameter. A higher maximal mean segmental dilatation and other raised compliance markers were found as AAA diameter increased [9]. The authors speculated this to be the consequence of elastin and collagen degradation and thus a marker for rupture tendency. On the other hand, Long et al. did not include a control group with non-aneurysmatic abdominal aortas. Also, the relationship with AAA outcome was left out, so they were not in the position to align their results with firm conclusions about rupture risk.

AAA development is not just bound by morphological variables. Researchers have found links between hemodynamic variables and aneurysm growth and rupture. Liu et al. constructed a new velocimetry technique, Echo Particle Image Velocimetry (PIV). They combined US with microbubbles acting as flow tracers in several cardiovascular models, including an AAA model. The authors managed to accurately measure several different complex flow patterns, like vorticity, stagnation and recirculation [10]. Recently, Zhang et al. performed a preliminary in vivo study using this technique in five human carotid arteries. Optical PIV is currently the gold standard for wall shear rate (WSR) and wall shear stress (WSS) measurement. Phase-contrast MRI also acts comparable to echo PIV in measuring WSR and WSS. When compared to the results of optical PIV and phase-contrast MRI, echo PIV measurements showed highly resembling error bars. This suggests echo PIV is a valid method for calculating WSS and WSR [11]. Development of this technique could lead to clinical reproducibility as a complement to US and may provide clinicians with hemodynamic information or prove useful in assessing WSS and its effects on aneurysm growth and rupture.

In the search for a more accurate diameter measurement, Van Essen et al. studied 22 AAAs with IVUS as part of preoperative assessment. IVUS seemed not only to perform as well as CTA, it also seemed "the most accurate way to determine the morphology of vascular structures (i.e., calcium, thrombus)" [12]. Previous to this research, White et al. already stated in their review article that IVUS is the ultimate tool for AAA assessment [13]. In spite of this, IVUS remains an invasive procedure that is far less available than

US, CTA, or MRI. Its use would be an addition to the current standard instead of an alternative, and whether the additional costs outweigh the potential benefits is still unclear. It therefore is unlikely that, in its current state, IVUS will have a great impact on AAA diagnostics.

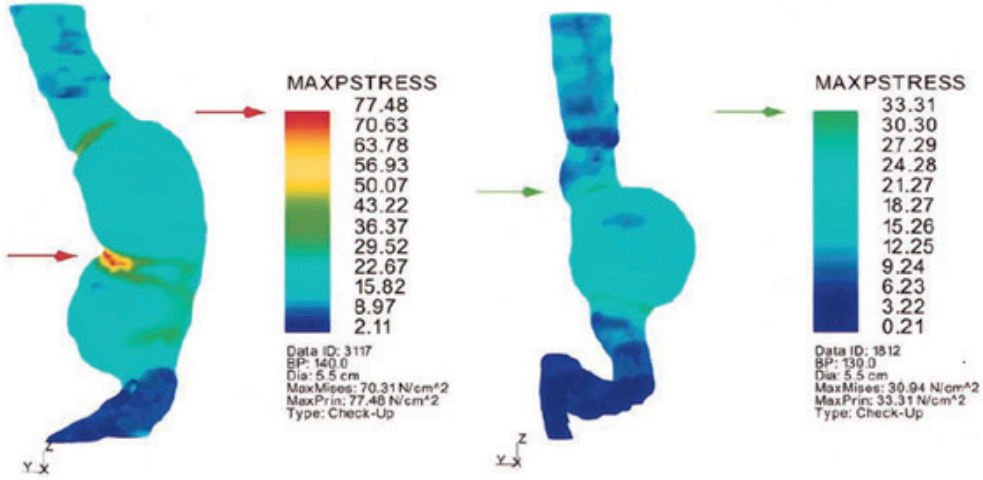
Computed tomography angiography

CTA is currently the first choice in determining the specific AAA anatomy for pre-operative assessment [14]. This choice revolves solely around its ability to render high-resolution images in acute and non-acute circumstances. US may perform well in screening, yet some specific morphological details are only presented by CTA. Exact size, width and length of the aneurysm are variable that are vital in preparing AAA surgery.

Though aneurysm diameter and growth are the major risk factors for rupture, other morphological details are being considered to be valuable in estimating the chances of AAA rupture. Not only the anatomical aspects of the vessel itself, but also their association to other tissues and vertebrae are likely to attribute to risk for AAA rupture. In a CTA based computational study, Fillinger et al. found an association between peak AAA wall stress and risk for rupture [15] (Fig. 1). In a later study, Fillinger et al. failed to find a significant correlation between thrombus size and AAA rupture in a non-computational retrospective CTA study [16] Speelman et al. opposed these results when their findings suggested a link between intraluminal thrombi and their influence on wall stress. Using computational interpretations of CTA scans, they discovered that an increase in thrombus size would increase the AAA growth rate, but would also be associated with lower wall stress [17]. Considering these ambivalent findings, the effects of intraluminal thrombus remain controversial.

AAA is known for its rigorous change in vessel anatomy. The aneurysmal sack grows in an unpredictable fashion with curving and sloping against the high intravascular pressure. These structural changes and concomitant thrombosis, calcification and atherosclerosis affect the dynamics of passing blood. But not only these pathological and incidental entities are a cause for damaging blood flow patterns. Inborn tortuosity of the vessel and otherwise physiologically formed anatomic structures might coincidentally result

Figure 1. Computational wall stress and rupture risk assessment in an AAA.



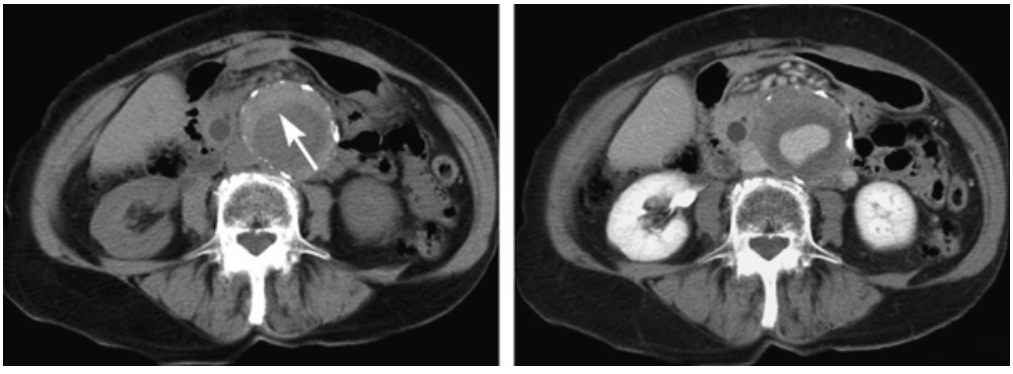
A three-dimensional model is recreated from raw computed tomography data. Wall stress is measured quantitatively and translated to a color gradient. Blue, green and red portray low, intermediate and high wall stress respectively14. (Reprinted with permission from Elsevier).

in damaging hemodynamics. For example, as the abdominal aorta follows the spinal curvature, the posterior wall is subjected to a higher hemodynamic stress compared to the anterior wall. An engineer perspective has been the mainstay in AAA risk assessment. The diameter criterion is based on the law of Laplace, though it is argued that the diameter plays only a partial role in the biomechanics of AAA. Its influence on rupture may be trivial in comparison to many other influences on the vessel stress and strength ratio [6]. Therefore, the focus has shifted towards computational AAA models for the evaluation of the different effects of vessel anatomy. Doyle et al. showed that asymmetric AAAs with localized wall thickness variation portray higher mechanical stresses and an increase of AAA rupture risk. They also theorized how the risk of rupture is connected to aneurysm diameter asymmetry. This might consequently influence the amount of wall stress on the posterior abdominal aortic wall. The asymmetry variation was calculated as the difference between the major and minor axes at the maximum width. The authors showed that increased asymmetry leads to increased posterior wall stress, implying future rupture. In respectively eight and nine out of 15 patients, diameter and diameter asymmetry was found to be significantly influential ($P < .05$) on posterior wall stress. Doyle et al. claimed that diameter asymmetry is on par with

current risk assessment using aneurysm diameter [18]. In an earlier retrospective cohort study by Fillinger et al., diameter asymmetry was calculated in CTA scans of two different AAA risk groups, elective versus ruptured. A significantly greater diameter asymmetry (P = .03; OR = 3.2) was found with patients receiving acute aneurysm surgery. Besides this, Fillinger et al. found minimized tortuosity of the aorta to be as influential as smoking and gender was on future rupture (P = .01; OR = 3.3) [23]. A number of promising software packages is being developed for the computation analysis of available CT and CTA images. Blood flow, pressure distribution, shear stress and the interaction of curvature, diameter asymmetry and intraluminal structures on any of these factors are part of a host of influences on the mechanics of wall deterioration and rupture proneness. We expect that this biomechanics-based perspective will be of great importance for future research.

A very different entity found in CT imaging is the flowing of contrast into the thrombus combined with transformation of the lumen. This might be the cause of a sign called hyperattenuating crescents (Fig. 2).

Figure 2. CT angiography images of a male patient with impending rupture of an AAA.



Bleeding into the intraluminal thrombus is portrayed in unenhanced (A) and contrast-enhanced (B) axial CT images as a crescentic form with hyperattenuation (arrow in A) [40]. (Reprinted with kind permission of D. Rakita, Department of Radiology, Division of Body Imaging, Long Island Jewish Medical Center, New Hyde Park, NY 11040, USA).

Histopathological testing showed this phenomenon to be hemorrhage into the thrombus and consequently, the aneurysm wall. Mehard et al. and Consalves et al. described a sign of impending rupture characterized by high-attenuating crescents in the AAA

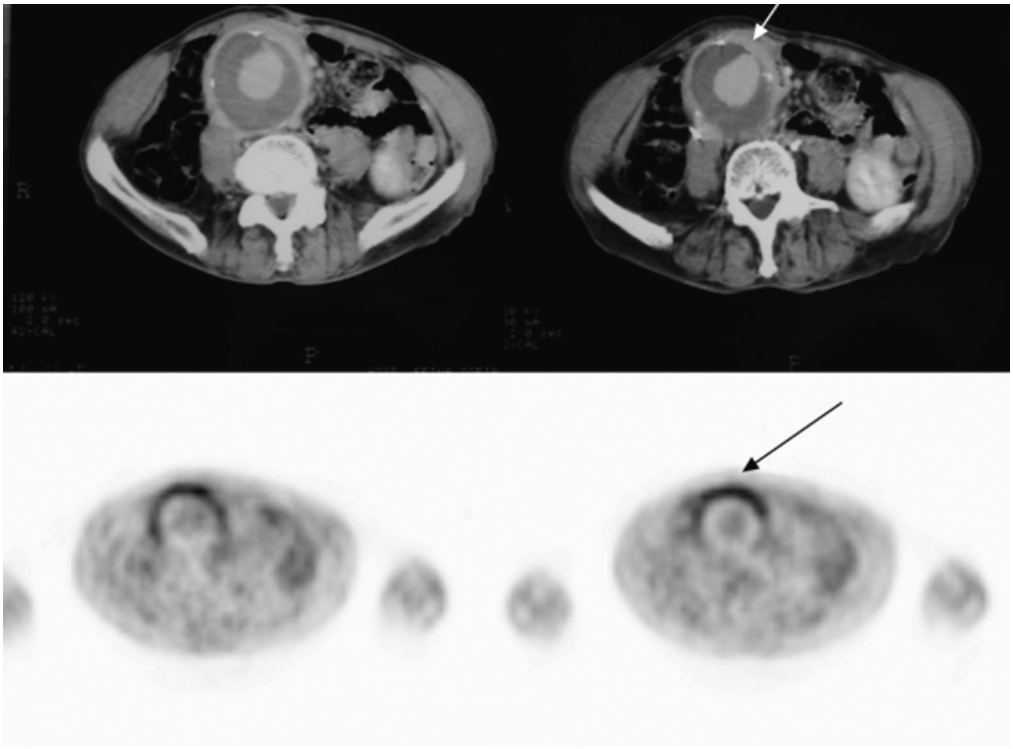
wall [19, 20]. Consalves et al. claimed the crescent sign to be of prognostic value for AAA rupture. In the study by Mehard et al., the specificity of high-attenuating crescents versus aneurysm complications was 93%. Hyperattentuation was defined by Siegel et al. as a signal being higher than contrast visibility of the psoas muscle in enhanced scans or a signal higher than that of patent lumen in unenhanced scans. In their study, 21% of patients with ruptured aneurysms showed hyperattenuating crescents, while no patients with intact aneurysms showed this sign [21]. Roy et al. most recently investigated signs of bleeding in the intraluminal thrombus and rupture site in AAA patients. Though the crescentic form was found significantly more in the ruptured group rather than the stable aneurysm group (38% vs. 14%; P = .02), localized areas of hyperattenuation were found in both groups without significant variation. There was, however, a significantly higher (P = .02) thrombus total attenuation in the ruptured group. Roy et al. compromisingly stated that "whether these findings also predict AAA rupture, remains to be established" [22].

PET-CT

Up until recently, only anatomically focused imaging modalities were used in risk assessment of AAA. The hybridization of PET-imaging with CT, provides added value over the separate use of PET and CT alone. PET enables functional imaging of cellular activity in AAA tissue, whilst the addition of CT grants improved anatomic localization and characterization. The radiopharmaceutical tracer 18F-fluorodeoxyglucose (FDG) is designed to image high-glucose-using cells. FDG accumulates in inflammatory sites due to its rich macrophage colonization. AAAs have also been proved to attract inflammatory cells and cytokines like matrix metalloproteinases (MMPs) [23]. Mycotic thrombus in AAA is a more severe infection of the AAA, often due to bacteremia or otherwise circulating bacteria. Mycotic aneurysms tend to rupture more easily and are known for a high mortality rate. Diagnosis of mycotic aneurysm is difficult, even on CT images. There are several suggestive signs, such as the presence of perivascular fluid or raised inflammatory blood markers, but none are either sensitive or specific enough in most of the cases. Recently PET-CT has shown to be very valuable [24]. PET-CT might also be able to provide information on short-term outcomes from pharmaceutical interventions on this infection (Fig. 3). In 2002, Sakalihasan et al. attempted to link FDG uptake with AAA using PET. After performing static whole-

body PET on 26 patients, 10 showed heightened activity in the abdominal aorta. Their preliminary research suggested PET has the capacity to portray metabolic activity within the aneurysm wall [25].

Figure 3. AAA images from CT (A, B) and 18F-FDG PET (C, D).



The arrows show how a region with high FDG uptake in the PET image coincides with a mural thrombus in the CT image[41]. (Reprinted with permission from Elsevier).

In 2008, through a highly significant ($r = 0.93$; $P < .0001$) association between 18F-FDG uptake and histologically assessed macrophage-density, Reeps et al. were able to confirm that vascular inflammation could be detected accurately using PET-CT. In symptomatic patients this activity proved to be significantly higher than in asymptomatic patients ($P < .001$) [26]. During the same year Sakalihasan et al. presented preliminary results of an ongoing research. In a patient group of 26 patients they found that subjects with positive PET scans (n=10) showed either AAA symptoms (n=5), expansion, leakage of blood and fulminant rupture (n=3). Two PET-positive

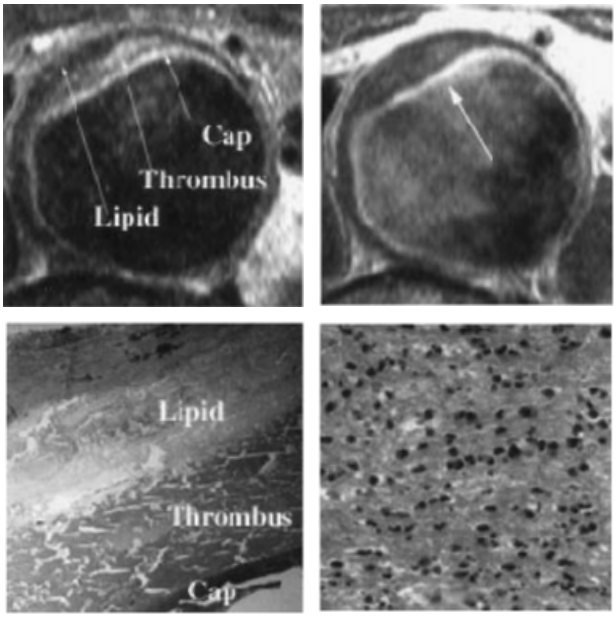
patients remained asymptomatic. Patients with negative PET images were treated after delay of several months out of convenience for the patient, without experiencing the adverse effects as seen in the PET positive patients. Consequently, the authors claimed that FDG-PET could provide an argument whether or not to justify an intervention [27]. In a longitudinal observational study, Kotze et al. most recently aimed to explain the relationship between FDG uptake and future growth rate of AAAs. Combined with US imaging, the expansion was measured after one year and associated with whole-vessel standardized uptake value (SUV). An inverse correlation of -0.501 (P = .011) was found between whole-vessel standardized uptake value (SUVmax) and aneurysmal growth. Two major study limitations were identified, however. Firstly, the follow-up lasted until twelve months. Secondly, the follow-up was performed using US which has an error margin that can be larger than small AAAs expand in a year. Nonetheless, the authors conclude their publication implying that less metabolically active aneurysms are more likely to grow and perhaps subsequently rupture [28]. These contradicting conclusions on the value of FDG undermine the results presented by both authors and might set back the research in this field.

However, FDG is not the sole imaging agent in PET-CT imaging of AAAs. Nahrendorf et al. investigated a modified dextran-coated iron oxide nanoparticle that particularly binds to macrophages. In a murine aneurysm model using ApoE -/- mice treated with Angiotensin II, PET-CT showed significantly higher signals from the AAA model (2.46 ± 0.48, standard uptake value) than in wild type littermates (0.82 ± 0.05, P < .05). Flow cytometry, immunohistochemical analysis and scintillation counting all portrayed how the nanoparticles migrated mainly to macrophages and monocytes within the AAA wall [29] Several other PET-CT reagents have been found in various medical fields such as interleukin-2 (IL-2), PK-12 and choline specific pharmaceuticals that could be applied in the field of inflammation PET diagnostics. It may only be a matter of time before these are introduced to AAA diagnostics. PET-CT is starting to prove its worth over CTA and US. Yet, the studies performed all suffered from having low amounts of patients in their cohorts and some authors questioned the reproducibility of their study. These results should therefore be regarded as preliminary.

MRI/MRA

Though MR is widely accepted as an imaging tool, its place within AAA diagnostics has not been established. Despite of this, multiple groups have been looking into the value of MRI and MRA in AAA risk assessment. In 1995, Prince et al. started assessing the usefulness of gadolinium-enhanced MRA for the diagnosis of AAA. It performed equally as well as CTA, without need of iodine-based contrast. This was a great improvement at the time, as renal complications due to the high iodine concentrations in CTA contrast were far more common [30]. In 2004 Kramer et al. used gadolinium-pentetic acid (DTPA) in identifying atherosclerotic fibrous caps in AAAs. Using T2-weighted MRI imaging, they managed to accurately delineate the fibrous cap and thrombus from the vessel wall (Fig. 4). Though the study was focused on identifying vulnerable atherosclerotic plaques, it consequently provided new insights on vulnerability of the AAA wall [31]. Also starting from an atherosclerosis-focused perspective, Sadat et al. linked MRI to AAA extracellular matrix degradation. Ultra-small superparamagnetic iron oxide (USPIO) particles are known for a strong interaction with macrophages and leukocytes. By observing the amount of USPIO uptake in the cells, which translates to lower T2- and T2* signal intensity, Sadat et al. theorized the phagocytic activity in the AAA wall could be quantified. In their study, T2- and T2* values in the AAA wall correlated significantly (Spearman's correlation coefficient = .90; $P < .001$) after injection with USPIO. This propensity to USPIO uptake by the aneurysm wall suggests inflammation is abundant. Utilizing this technology, it seems increasingly feasible to quantify inflammation and concomitantly to quantify stability of the AAA. Regrettably, there was no histological control for these findings, but as a feasibility study it provided encouraging results for larger cohort studies [32]. Nchimi et al., however, did manage to provide histological backgrounds to their in vivo USPIO MRI study. Post-USPIO signal-to-noise ratios for thrombus tissue and muscle tissue were significantly different ($P = .016$), as were the contrast-to-noise ratios for the luminal sublayer of the thrombus ($P < .001$) and deeper thrombus ($P < .012$).

Figure 4. MRI and histology images of an AAA.



A T2-weighted MRI image (A) and T1-weighted MRI image after Gd-DTPA infusion (B) of an AAA with intraluminal thrombus shows three distinct layers. These components were confirmed by histopathology (C). The fibrous cap contained high numbers (120 white blood cells/hpf) of polymorphonuclear leukocytes, as was seen using high power field microscopy (D) [30]. (Reprinted with permission from Elsevier).

Using USPIO as a phagocytosis-specific imaging agent, accurate morphological assessment of the thrombus can be achieved by visualizing phagocytic activity corroborating with immunohistochemical stainings. CD66b (polymorphonuclears), CD68 (macrophages) and pro-MMP-9 (extracellular matrix remodeling) were found in significant levels ($P = .009$; $P = .002$; $P = .014$; respectively) opposed to a decrease in signal intensity of the luminal sublayer of the thrombus. USPIO is known for a high rate of liver clearance. It is therefore questionable whether the low signal intensity was entirely due to high macrophage uptake or whether it was partly due to the rapid clearance [33]. Sadat et al. also stated that the USPIO agent used in their study is no longer commercially available. Therefore, repetition of this research is highly improbable. Acknowledgement through other studies with larger cohorts, repeating or enriching this research is essential, as both authors state their research was bound by the limited amount of included patients.

Bio-optical imaging

Bio-optical imaging uses techniques such as chemiluminescence, bioluminescence and near infrared fluorescence (NIRF). As of yet, bio-optical imaging of AAA has only been used in experimental settings. Luminescent probes react to a chosen substrate (e.g. MMP, VEGF) by proteolytic cleavage of the substrate and consequently emit fluorescence. Intensity of the signal is therefore directly correlated to the substrate concentration in the imaged tissue. As inflammation seems likely to be involved in AAA growth and rupture, more and more individual factors are being discovered. Inflammation-induced elastin degradation in the extracellular matrix has been shown to be of influence on AAA development. The main actors in this process seem to be MMP-2, MMP-9 and their counter actor tissue inhibitor of metalloproteinase-1 (TIMP-1) [34]. Kaijzel et al. proposed a new method of AAA identification, using MMP-specific probes in fibulin-4 reduced-expression allele mice. Fibulin-4 is relevant in the organization of extracellular matrix structures and regarded an important factor for arterial integrity. Though mainly affecting the ascending and descending thoracic aorta, this specific knockdown perpetuates aortic aneurysm dilatation in more and less severe degrees for homozygous (R/R) and heterozygous (+/R) knockdowns, respectively. Using a NIRF imaging system, a dose-dependent rise in MMP fluorescence was shown in the +/R (1.79-ns life-time) and R/R (2.02-ns life-time) mice versus the control littermates (<1-ns life-time). After whole mouse scanning, individual hearts and aortas were harvested and scanned for MMP. Control mouse aortic arch MMP signal intensity reached 19.75 relative fluorescence units (rfu), whilst increased rfu (26.53 and 105.77) were measured in +/R and R/R mice, respectively. Using histological analysis, zymography and fluorescence molecular tomography, similar results were found. The authors suggested that NIRF imaging of MMP could provide information on aneurysm development in the thoracic aorta [35].

Neovascularization has also been proposed to be of value in aneurysm pathology. Non-aneurysmal aortas and intact aneurysms demonstrate a lower degree of mural neovascularization than ruptured aneurysms [23]. Vascular endothelial growth factor (VEGF) is a major pro-angiogenic mediator. Tedesco et al. sought to associate VEGF receptor (VEGFR) expression with aneurysm development in AAA in an Apolipoprotein E-deficient (Apo E -/-) murine AAA model. These murine models developed suprarenal

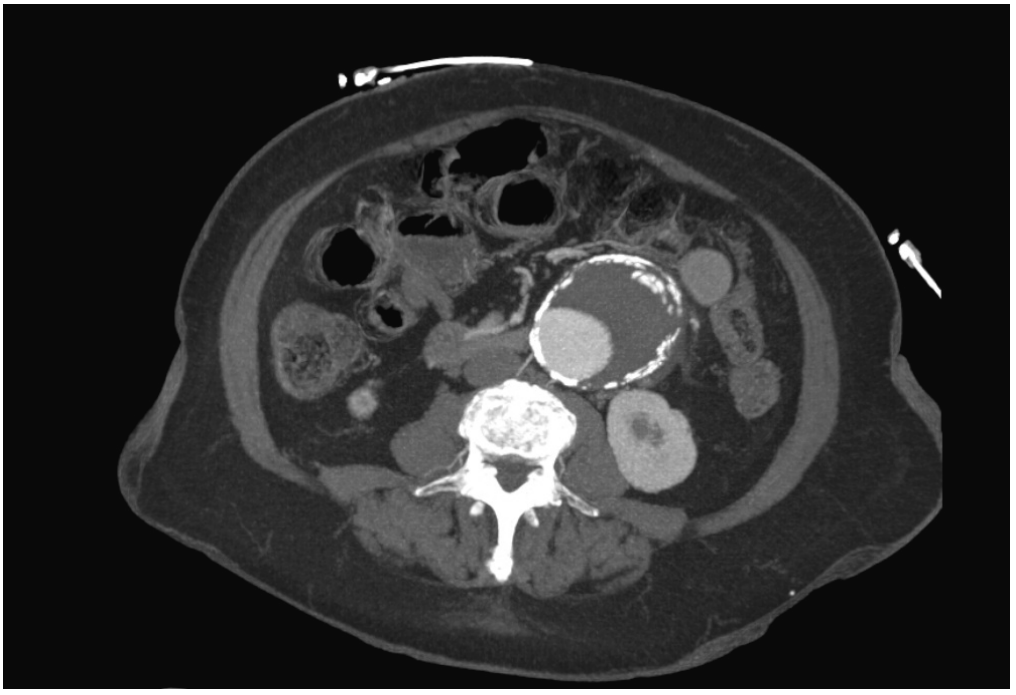
AAA after infusion with Angiotensin II (Ang II mice). Selected mice were given either angiogenesis inhibitors (Exel 0862) or doxycycline (positive control), which is known to limit experimental AAA progression [36]. Empty vehicle was given as a control to others and inactivated VEGF probes (scVEGF/in) acted as a control for non-receptor mediated reactions. NIRF imaging resulted in significantly higher VEGFR signal intensity for aneurysmal aortic segments in relation to non-aneurysmal segments in Ang II mice and control mice and Ang II scVEGF/in mice. This association was confirmed by fluorescence microscopy. Also, angiogenesis inhibition seemed to significantly limit AAA growth in controls versus Exel 0862 and doxycycline. Mural inflammation too correlated significantly in Exel 0862- and doxycylin treated mice versus control vehicle-treated mice. The authors concluded that VEGFR has definitive experimental value as a parameter for aneurysm progression. In the eventual case that these results may translate to human pathology of AAA, this research may provide new diagnostic options in the form of bio-optical imaging [37].

DISCUSSION

There seem to be many contenders for validation of AAA rupture risk. Unfortunately, most of the preliminary and introductory studies that have been performed lack scientific strength. Often this was due to small or unbalanced cohort population size. Studies focused on clinical implementation seem to be the heart of AAA research. Their main goal is to enhance the diagnostic capabilities of already existing imaging modalities. This clinically-focused research clusters known clinical entities, variables and comorbidities and checks off against endpoints like aneurysm growth and rupture. Except for smoking, familial occurrence, vessel tortuosity and diameter asymmetry, most experimental variables were rejected as a risk factor for AAA rupture. Calcification is a clinical entity that has received little scientific attention (Fig. 5)

Just as thrombosis, the effect of calcification on the integrity of the abdominal aorta seems ambiguous. Calcification decreases elasticity and compliance of a vessel. It can therefore be hypothesized that calcification adversely affects the vessel's reactivity to stress and as a consequence increases rupture risk [38]. Abdominal aortic calcification has also been associated with vascular morbidity and mortality [39]. Contrary to these

Figure 5. CT image of a female patient with a symptomatic non-ruptured AAA.



Calcification was found along the complete circumference of the vessel. The high-density signal is distinctly visible in spite of the contrast agent in the lumen.

statements, using US, Lindholt et al. showed an increase of calcification would reduce the need for intervention, suggesting calcification has a protective role. Still, until now, little else than computational calcification measurement studies have been focusing on the meaning of calcification. This lack of research on the subject is theorized to be due to several limitations in CTA scans of AAAs. The Agatston score is currently regarded as the best validated method in coronary calcification measurement. However, the Agatston score is inapplicable in standard AAA CTA scanning. Since CTA uses contrast fluid to identify the abdominal aorta, a background signal is produced that floods all intravascular high-density particles. Non-contrast CT scans are of little value in vascular imaging and it is questionable whether performing both a non-contrast and contrast CT is justifiable since this will double the radiation exposure. The lack of methodology to investigate calcification in CTs needs to be overcome for this specific field of interest to be accurately investigated. Dual-energy CT (DECT) might provide

an alternative. DECT uses two different tube voltages which could be set to both the absorption rates of calcium and soft tissues like blood vessels. It therefore could bypass the "contrast contamination". This highly applicable update to common CT imaging needs further investigation and validation, but its potential should be recognized. Results of these studies might be implemented both inexpensively and highly feasible in medical practice.

Research in this field is limited to the boundaries of existing modalities. Yet experimental imaging modalities and substrates can go where existing modalities fall short. For example, the highly specific, radiation independent imaging of human biomarkers for AAA risk holds great promise. Bio-optical imaging, however, is still limited to laboratory studies as both the modalities as the reagents are in many ways unsuitable to be used in humans. Further development that focuses on creating beneficent materials will improve practicality and might propel this field to new heights. Experimental utilization of MRI and PET-CT seem to be the most promising new lead in AAA diagnostics. Their dual function of both anatomical and functional imaging of the abdominal aorta is a contribution and not an alternative to the institutionalized US and CTA in AAA diagnostics. Of value may be the next generation PET-MRI camera for simultaneous imaging of anatomy and function. The merits of also being able to measure biochemical, inflammatory, metabolic activity, apoptosis and angiogenesis are highly significant. Fluctuation in inflammation and metabolism may provide a better instant understanding of pharmaceutical interactions with AAA or wall weakening on a much shorter term. This is in stark contrast to US screening of AAA growth, which is valuable only if repeated every six months. Nevertheless, a study by Osman et al. showed how clinically significant findings such as cirrhosis, kidney lesions and AAA on the CT portion of PET-CT were not shown by PET or combined imaging [40]. Though these findings are incidental, major diagnoses might be overlooked if CTA interpretation moves to the background.

Fact remains that currently, aneurysm diameter is the only criterion clinicians can rely on, even though this is rapidly being considered to be less so. The amount of unnecessary interventions for AAA repair and the degree of risk taken when approaching a small aneurysm with watchful waiting are equally unknown. We believe that an expansion of

the current paradigm surrounding the AAA diameter towards a broader interpretation of biomechanical influences, will be the next step in the prediction of AAA rupture. Randomized clinical trials with any of these methodologies or risk factors may still only be a future prospect, but eventually their intellectual offspring might provide a broad yet accurate screening protocol for the risk assessment of the AAA.

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2.2

Aortic calcification and rupture risk

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(Vascular and endovascular consensus update. Greenhalgh RM (ed.). BIBA Publishing, BIBA Medical Ltd, London, 2014, 179-188)

INTRODUCTION

Current risk assessment of abdominal aortic aneurysm (AAA) is based primarily on the maximum diameter of the aneurysm. Diameter has been chosen to function as predictor for rupture based on the Aneurysm Detection and Management (ADAM) trial and the United Kingdom (UK) Small Aneurysm Trial [1,2]. Surgical aneurysm repair is considered justified as long as the risk of rupture outweighs the risk of the intervention itself. Adding risk factors, such as female gender, age, and AAA prevalence in the family can predict rupture more accurately [3]. It has also become clear that tobacco smoking has a dose-dependent correlation to the development and growth of an AAA [4]. Although all of these clinical risk factors have been identified and widely used, very little is known about why small aneurysms rupture "prematurely" and why some aneurysms grow far beyond the known threshold for intervention without rupture [5]. With this in mind, relying mainly on the diameter criterion seems limited, as it will not be able to discriminate which AAA is prone to rupture. Rupture risk assessment of small aneurysms (3.5 – 5.0 cm) could be fine-tuned by adding more risk factors.

Both endovascular aortic repair (EVAR) and open repair suffer from a number of re-interventions and peri- and postoperative complications. Therefore, lowering the diameter threshold might lead to a larger number of unnecessary interventions [6]. It remains unclear what percentage of patients receives unnecessary surgery. To enhance the potential of current AAA rupture risk assessment, new risk factors should be added [5]. In coronary artery disease, the prognostic potential of calcification has been studied extensively and even though the pathophysiological processes are different, there seems to be a strong link between aortic calcification and cardiovascular morbidity and mortality [7,8]. However, much less has been described regarding the local effects of calcification on the arterial wall. Some have argued that calcification is a sign of wall degeneration due to inflammation and might therefore lead to aneurysm rupture [9-11]. Others proposed that increased calcification could lead to less rupture as calcification might act as a shielding mechanism. Despite this lack of consensus regarding the exact pathophysiology, it cannot be ignored that the relation between the integrity of the abdominal aortic aneurysm wall and the degree of calcification should be investigated more extensively.

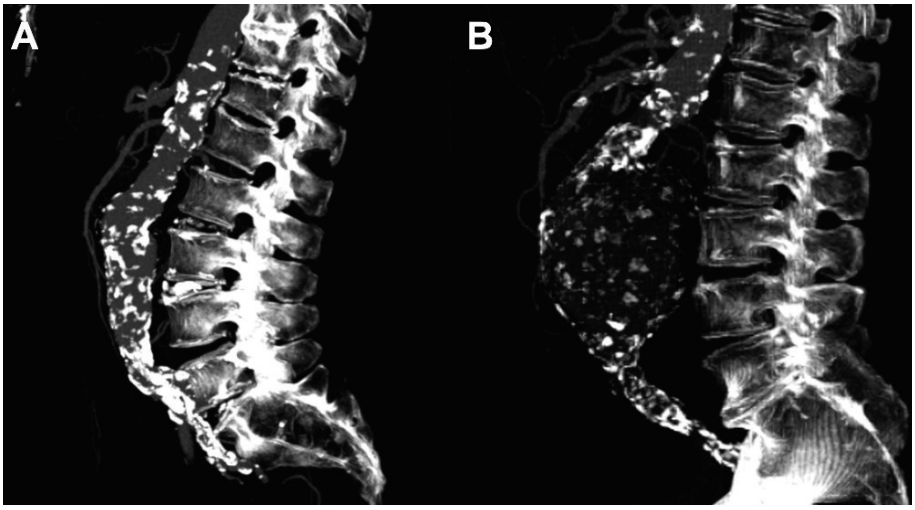
Vascular calcification

An atherosclerotic process initiates the formation of calcification in the arterial wall. The trigger of this process is endothelial dysfunction as a consequence of local cardiovascular risk factors such as high blood pressure or reactive oxygen species concentrations accelerated by smoking [5]. Macrophages migrate towards the lesion sites and introduce cytokines that further initiate inflammatory processes, followed by increased migration of macrophages. Smooth muscle cells will be stimulated toward osteogenic differentiation by the pro-osteogenic cytokines that follow in the stead of the macrophages. The newly formed osteoblast-like cells deposit calcium and form micro-calcifications. These small regions of calcium, also known as "spotty" or "soft" calcification continue the vicious cycle through more intense inflammatory activation of surrounding cells. After many cycles of calcium deposition and inflammation, a solid calcified "plaque" is formed. As long as the inflammation process is at its peak, it will attract wall integrity degrading proteases such as matrix metalloproteinases, collagenases, and elastases [9-11]. Studies in mouse-models have suggested a role for circulating calcium-chloride and calcium-phosphate in the formation of calcification. Though the aneurysmal development in the mouse-models was artificial, the aneurysm wall seemed histologically comparable to that of human tissue [12, 13]. Some aspects of these theories are still speculation and much more should be known regarding the biological aspects of aortic calcification before consensus can be defined.

Relevance

Very little research has been performed regarding the role of calcification in the abdominal aortic aneurysm wall. The lack of research may be caused by its multifactorial etiology, as there are several elements related to AAA calcification that need attention. First, calcification is clearly visible on computed tomography (CT) and x-ray images as structures with high attenuating signals (Figs 1A and 1B).

Figure 1. Sagittal projection of the vertebrae and abdominal aorta on CT.



Despite the small aneurysm size (<5.0cm), severe calcification is found alongside the vessel wall (A). In a different patient with a clearly enlarged aneurysm, much calcification is found alongside the wall (B).

Attempts to quantify vascular calcification are numerous [14]. Although calcification is easily visualized, it is hard to quantify. Many have tried to measure the degree of calcification, such as a volumetric scale or as a percentage of the wall circumference, as well as several other semi-quantitative scores [15,16]. As described above, the most important aspect of arterial calcification is the inflammatory process that follows up to be a vicious cycle of more calcification and more inflammation. Calcification might be a marker for a sustained inflammatory state of the local vessel wall. Consequently, it could also be a marker for the frailty of the aneurysmal wall tissue. However, there are also signs that extensive calcification or solid calcified plaques are more likely to be protective against further degradation of an already weakened wall. Though a long process of inflammation precedes the formation of a solid calcified plaque, the inflammation decreases as the calcification becomes more extensive. Also, one could hypothesize that dens tissue such as calcified vessel wall is not a structural weakness, but a strong layer that shields the weakened underlying intimal and medial wall. In a study by Lindholt [17], the degree of calcification was classified as > 50% or < 50% calcification of the circumferential wall of small aneurysms. The results showed that patients with a more than 50% calcified circumferential wall tend to have slower expansion of the aneurysm and less need for subsequent surgery. Regrettably, this

study did not include aneurysm rupture as an outcome. This illustrates the lack of definitive conclusions regarding the potential protective role of calcification compared to the stronger evidence of the disruptive capabilities of microcalcifications. It seems highly likely that calcification is correlated to aneurysm rupture, whether it be due to its disruptive or protective effects of calcification on the arterial wall. To our knowledge, very little has been published on this topic, although many studies have investigated abdominal aortic calcification in respect to other topics, such as anastomotic leakage after colorectal surgery, female depression, and dialysis treatment.

Measuring AAA calcification

Calcification is an easily visualized on most imaging modalities. As CT scanning is currently the best available imaging modality to visualize abdominal aortic aneurysm features, it has frequently been used to quantify calcification [5,14]. Generally, three methods have been employed in the analysis of vascular calcification. The first is based upon the Agatston score used in coronary artery calcification scoring.[18] This method counts calcifications as a function of the amount of voxels with a certain degree of signal intensity. Four degrees are identified and with each increasing degree the score is multiplied or "weighted". The higher the signal intensity and the higher the amount of voxels, the higher the calcification score becomes. As this method has been tried and tested under numerous circumstances in the coronary arteries, it seems a logical step to apply this method in larger vessels such as the abdominal aorta. The drawback of this method is that it is unreliable in contrast-enhanced images. The Agatston score works through rigorous thresholds for signal intensity. Yet under contrast-enhanced circumstances, these thresholds are greatly surpassed by the contrast signal intensity.

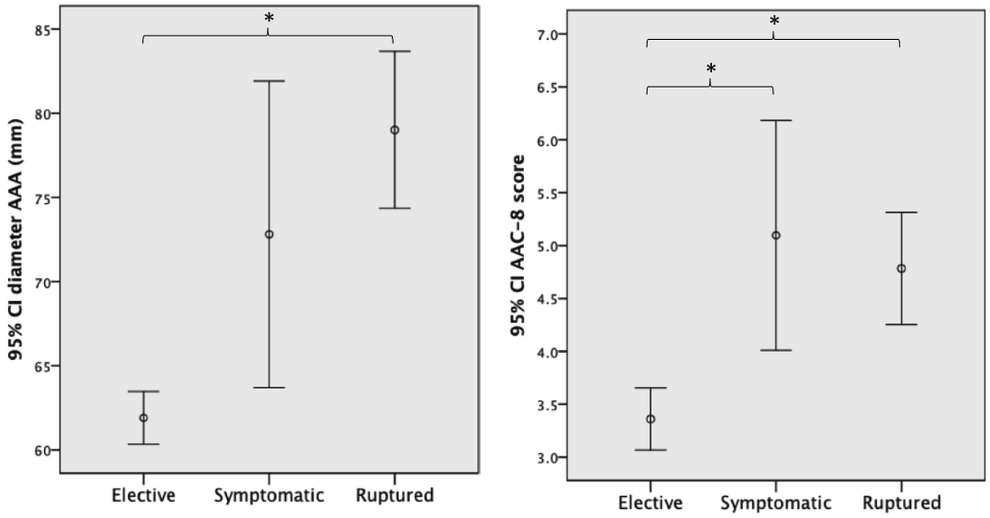
A second method for calcification scoring is to measure the absolute volume of the calcified spots [15]. This method is highly comparable with the Agatston scoring technique. Instead of choosing a weight to each score, one simply multiplies the amount of voxels above a certain threshold with the volume of each voxel. This method should be able to be used universally, as the volume of a calcification is an absolute value expressed in cubic millimeters. Studies have shown that coronary artery calcification scoring can be performed in the presence of intravascular contrast [19,20]. One commercial package claims to be able to quantify calcification in the abdominal aortic aneurysm though, to our knowledge, no validated studies have been published [21]. A different approach

is through less quantitative methods like the abdominal aortic calcification scores. On either a 24- or 8-point scale, calcifications are counted manually [5,22]. The abdominal aortic calcification 24-score (AAC-24) starts with the identification of the abdominal aorta alongside the lumbar vertebrae L1 to L4. By dividing the aorta in three regions per lumbar vertebra, 12 anterior and 12 posterior regions can be distinguished. The degree of calcification is then counted as either present or absent in each of these regions. The resulting score lies between 0 and 24. The AAC 8-score is counted per vertebra on the posterior and anterior side instead of dividing each vertebra in three regions. These scores benefit from being simple to use in x-ray and CT images, without the use of measurement algorithms and this method can be applied in contrast enhanced images. Lastly, calcification can be measured as a percentage of the surrounding tissues. By measuring calcification as either a percentage of the wall circumference [16,17], a percentage of the total aneurysm volume, or a percentage of the lesion surface area [23], one is able to measure calcification whilst correcting for other anatomic variables and most importantly, for aneurysm diameter.

Calcification in electively versus acutely repaired aneurysms

In a recently published study by our group, the first evidence was found regarding the correlation between calcification and abdominal aortic aneurysm rupture [24]. In this study, two relevant groups were distinguished as case and control groups. The case group consisted of 68 patients with acutely ruptured aneurysms and 23 with symptomatic aneurysms with a high impending rupture risk. The control group of 230 patients existed of an age- and gender-matched population of patients who underwent elective repair based on the aneurysm diameter. The degree of calcification was measured on pre-operative contrast-enhanced CT scanning images. For the measurement of calcification, the abdominal aortic aneurysm-8 score was used, as described earlier in this chapter. Also, other relevant clinical and demographical data were collected for each of the patients. Although most of these covariates were equally distributed over the case and control groups, only the calcification score and the aneurysm diameter were significantly higher in the case group. Odds ratios for rupture increased by 1.062 (95% confidence interval (CI): 1.042 – 1.082; $P < .001$) for each millimeter increase in diameter. For each point increase in calcification score the odds ratios for rupture were 1.35 (95%-CI: .15 - 1; $P < .001$). (Figs 2A and 2B)

Figure 2. Bar graphs of the AAA diameter and AAC-8 score.



In (A, left), the 95% confidence interval of the mean bar graph of AAA diameter size for elective, ruptured, and symptomatic AAAs is given. In (B, right) the 95% confidence interval is given of the mean bar graph of the AAC-8 score for elective, ruptured, and symptomatic AAAs.

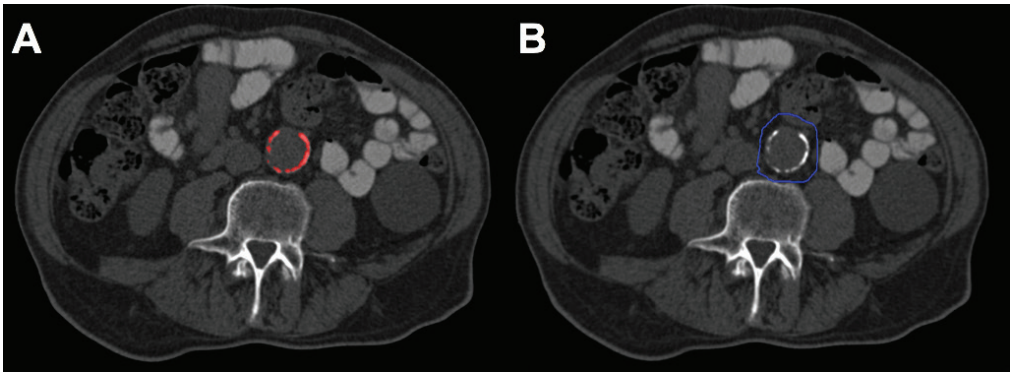
We also showed that the aneurysm size had marginal effects on the calcification score, by comparing calcification scores in low- versus high-risk aneurysm diameter groups. Further studies on this topic should include stringent matching for aneurysm diameter, to investigate its confounding effect. And though a causal correlation can never be made in a retrospective study, these results have established that there is a role for calcification in the diagnostics of AAA.

FUTURE PROSPECTS

Before abdominal aortic aneurysm calcification becomes an established risk factor for rupture, more aspects of this entity should be studied. Currently, dialogue on calcification is only based on one study with a 3b level of evidence [24]. The other relevant studies cited in this chapter provide a theoretical background but are not suited to link calcification as a cause for aortic wall weakening [1-20]. However, research that could propose opposite arguments are yet to be published. Therefore, it should be the goal to further study the clinical value of calcification, and in parallel, study

its biochemical and pathophysiological workings. A validated method of calcification measurement should be established to guarantee low inter-observer variability (Figs 3A and 3B).

Figure 3. Computational analysis of AAA calcification with commercially available software.

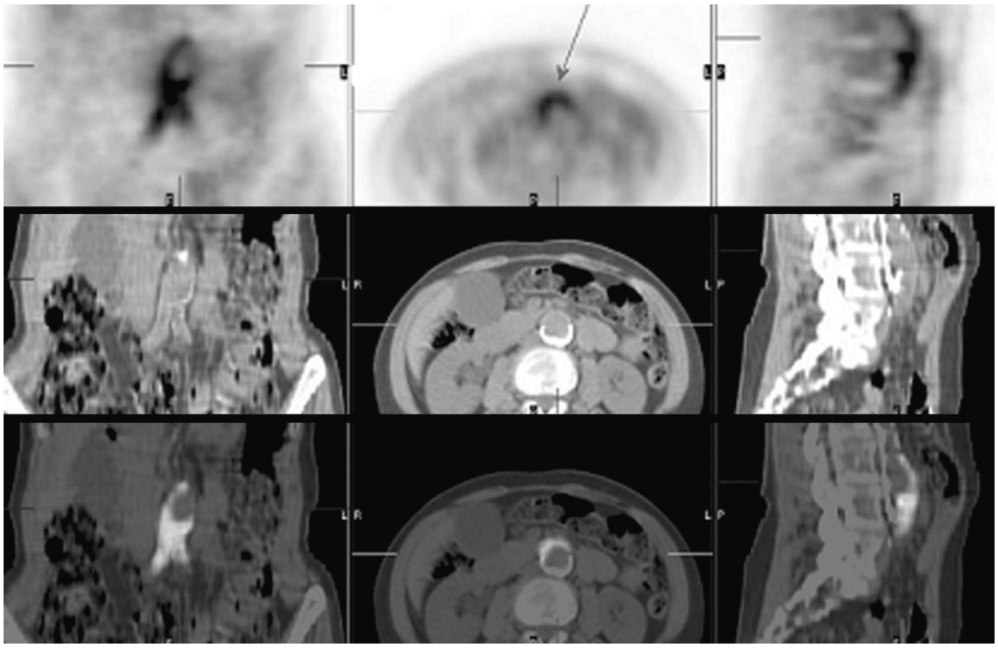


A blue region of interest is drawn by hand in which the calcification volume is measured (A). The red colour highlights the automatically identified calcification spots (B).

Computational analysis is currently the best approach for accurate measurements. Despite the fact that this step has not yet been finished, other approaches have already been proposed that can assess the effects of calcification without quantification. Several publications in the field of biomechanics propose a role for anatomical entities within the abdominal aortic aneurysm. As the aneurysm sack is host to complex hemodynamic forces, one can imagine that these forces have other effects than that of the expanding diameter. Hemodynamic shear stress of the aneurysm wall is believed to deteriorate the wall structure and instigate an inflammatory process [25-28]. Like thrombus, calcification is an anatomical entity that occupies a portion of the vessel, interfering with local hemodynamics consequently leading to wall damage. On the other hand, it might as well shield the aneurysm wall from locally disruptive shear and tension stress. The methodology for this type of measurements is becoming increasingly available and several researchers are already working on the topic of shear stress [25-27]. Hopefully, more research will be invested to elucidate the role of calcification in this field. Another imaging modality that has high potential for quantifying the effects of calcification is positron emission tomography (PET) using 18F-sodium fluoride (NaF) tracer. This tracer is an established agent that is able to visualize and measure the degree of early

bone formation and tissue remodeling. Studies with 18F fluorodeoxyglucose (FDG) already showed the inflammatory state of an abdominal aortic aneurysm [29-31]. The research performed by Truijers et al. [31] however shows a clear discrimination of the calcified region and the inflammatory active region of the aorta. In a recent study by Dweck et al. [32], the coronary artery calcification score was linked to a raised 18F-NaF uptake. Active calcification was also correlated to an increased 18F-NaF uptake. it is expected that similar research will be performed in the evaluation of abdominal aortic aneurysm. (Fig. 4)

Figure 4. CT and 18F-FDG PET images of the abdominal aortic aneurysm.



The top row shows the 18F-FDG PET images of the abdominal aortic aneurysm. The second row shows the CT images at the same position. In the lower row, the FDG-PET and CT images are fused. From left to right are the coronal, axial, and sagittal views of the abdomen. On the anterior side of the aorta, inflammatory activity is shown in the axial view of the top (arrow) and lower row, without calcification (mismatch). The middle and lower row show a large calcified layer on the posterior aortic wall [31].

CONCLUSION

This chapter challenges several arguments for more extensive study of the abdominal aortic aneurysm rupture risk. Abdominal aortic aneurysm pathophysiology is an insufficiently highlighted topic in the field of vascular surgery. Plentiful evidence suggests that diameter alone in the assessment of the abdominal aortic aneurysm is insufficient. Though this chapter mainly focuses on calcification, the rupture risk assessment will be improved by adding risk factors originating from other anatomical entities within the aneurysm, local acting biochemistry, and genetics. The additional scientific progress made in the field of molecular imaging should clarify both the anatomical and physiological effects of calcification on the AAA wall. In the meantime, it is important to agree upon a reliable method of AAA calcium quantification. This will allow for better comparison between studies and potentially a practical application for the vascular clinician. From a number of different perspectives, it has become clear that there is an inflammatory component to vascular calcification that could propagate the aneurysmal development of the abdominal aorta. Others emphasize that calcification in its fully developed end-stage might also protect a weakened aortic wall from further deterioration. Whichever theory is true, quantification of local calcification might provide another step forward in AAA diagnostics and prognostics.

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Chapter 3

Abdominal aortic aneurysm rupture risk and calcification; clinical research

3.1

Calcification as a risk factor for rupture of abdominal aortic aneurysm

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(European Journal of Vascular and Endovascular Surgery 2013;46:542-8)

ABSTRACT

Objectives: Abdominal aortic aneurysm (AAA) is a major cause of death in developed countries. The AAA diameter is still the only validated prognostic measure for rupture and therapeutic interventions are initiated accordingly. This still leads to unnecessary interventions in some cases or unidentified impending ruptures. Vascular calcification has been validated abundantly as a risk factor in the cardiovascular field and may strengthen the rupture risk assessment of the AAA. With this study we aim to assess the correlation between AAA calcification and rupture risk in a retrospective unmatched case-control population.

Methods: A database of 334 AAA patients was evaluated. Three groups were formed: elective (eAAA; n = 233), ruptured (rAAA; n = 73) and symptomatic non-ruptured (sAAA; n = 28) AAA patients. The Abdominal Aortic Calcification 8 score (AAC-8) was used to measure the severity of vascular calcification.

Results: The AAA diameter (61 ± 12 mm vs. 74 ± 21 mm; P < .001) and AAC-8 score (3.4 ± 2 points vs. 4.9 ± 2.3 points; P < .001) of the eAAA and the combined rAAA and sAAA groups, respectively, were significantly different after univariate analysis. Multivariate analysis showed that larger AAA diameter (OR: 1.048/mm increase; 95%-CI: 1.042 - 1.082; P < .001) and a higher AAC-8 score (OR: 1.34/point increase; 95%-CI: 1.19 - 1.53; P < .001) were significantly associated with developing into a sAAA or rAAA. Peripheral artery disease was significantly correlated to eventual elective treatment (OR: .39; 95%-CI: .15 – 1; P = .049).

Conclusion: This study suggests a trend of an increased degree of calcification in symptomatic or even ruptured AAA patients as compared to elective AAA patients.

INTRODUCTION

AAA is a major cause of death in Western countries with over 8,000 reported deaths in the United Kingdom annually. Acute rupture may lead to death in up to 90% of patients and 40-70% of these patients who receive surgery will not survive. Also, the 30-day post-operative mortality has been reported being 6% after elective surgery versus 37% after emergency surgery [1,2]. In its current state, risk stratification of AAA is solely based on the maximum diameter of the abdominal aorta. However, the importance of the aortic diameter has come under debate in recent literature [3,4]. Though diameter is predictive of rupture in large population studies like the United Kingdom Small Aneurysm Trial [5] and the Aneurysm Detection and Management trial [6], it reflects poorly on individual risk assessment. It has become questionable whether a large aneurysm diameter alone is sufficient to justify intervention. On the other side of the spectrum, the rupture risk analysis of small aneurysms (3.5 - 5.0 cm) is being reconsidered as this particular patient group could suffer from preventable rupture. However, the risks of re-intervention, complications including death, and of unnecessary intervention remain a clear threat for both endovascular (EVAR) and open surgical repair. To enhance the potential of current AAA rupture risk assessment, new potential risk factors should be added. Additional risk factors have already been identified and tested intensively, although just a few remain promising for clinical validation [4]. The prognostic value of calcification has been described extensively in cardiovascular risk assessment [7]. Calcification has been shown to be a sign of a degenerative inflammatory process involved in the arterial wall [8-11]. For that reason, we hypothesize that the risk of rupture is associated with the degree of calcification of the AAA. Arterial calcification has had little attention as a risk factor in AAA diagnostics. For the largest part this is due to a lack of validated calcification measurement tools for clinical application. Though computational analysis of calcification of the coronary vessels has been validated rigorously, no such tool has been developed for larger vessels such as the abdominal aorta. In this study, a visual calcification grading tool, the AAC-8 score, will be employed for the scoring of standard care abdominal computed tomography angiography images. The aim of this study was to assess whether aneurysm calcification is correlated to rupture in a retrospective unmatched case-control population.

MATERIALS AND METHODS

Study design

All patients diagnosed with an AAA from the start of 2005 through 2011 were retrospectively collected from a central patient database at the Department of Surgery (Division of Vascular Surgery) at our center. During this period, 911 patients were considered for treatment of AAA. Three groups of patients were distinguished on the likelihood and event of rupture. The elective group (eAAA) consisted of patients who had received elective surgery following an AAA diameter measurement of over 5.0 cm or 5.5 cm for female or male patients respectively, or AAA growth over 5 mm within six months (n = 780). The symptomatic group (sAAA) was comprised of patients who had been diagnosed with an AAA on CT (n = 32). These patients received CT imaging based on having lower back pain, tenderness of the abdomen or a pulsating abdominal mass that was painful on palpation, without signs of rupture. The ruptured AAA group (rAAA) contained patients who had been diagnosed with having acute signs of rupture, such as hypotension and retroperitoneal hemorrhage on either computed tomography angiography (CTA) or during operation (n = 99). CTA scans of 28 sAAA and 73 rAAA patients were acquired. As a control group, 233 eAAA patients were collected from the database. The following common clinical and demographic variables were included in our analysis: AAA diameter, gender, age, body mass index, systolic, diastolic and mean arterial blood pressure and serum creatinine levels. For all patients, these variables were collected and measured by independent clinicians in the non-critical setting. Age- and gender matching was performed based on this information (Tables 1 and 2). After matching, five sAAA and five rAAA patients could not be matched to control patients and were excluded. Of the eAAA patients, three could not be matched to case-patients and were also excluded. For eAAA patients, this was the day before intervention. For sAAA and rAAA patients, this data was collected from the last non-critical measurement within one year before the intervention. These were performed either at hospital admissions or during routine check-ups by general practitioners. In some cases, serum creatinine levels of sAAA and rAAA patients could not be collected because these criteria were not met. The following comorbidities were also screened for: diabetes mellitus type 1 or 2 (DM) [12], chronic obstructive pulmonary disease (COPD) [13], known cardiovascular disease (CVD) [14]. CVD was defined as

either one of the following illnesses. First of all, coronary heart disease (CHD), either in the form of angina pectoris, myocardial infarction, heart failure or death due to CHD. Cerebrovascular disease such as transient ischemic attack and stroke were also regarded as CVD. Though peripheral artery disease (PAD) and thoracic, femoral, iliac and popliteal aneurysms are also regarded as CVD, we separately studied the distribution of these clinical entities. Information on smoking history, family history of AAA, and history of hypertension was also collected. A family physician or a specialist diagnosed DM, COPD, CVD and hypertension previous to this study. At >1 cigarette daily at least 1 year prior to the AAA repair, a patient was classified as a smoker. To some extent, all of these factors are known to affect cardiovascular risk and were therefore included to correct for confounding [15-17]. All AAA in this study were classified by their diameter by independent radiologists prior to the study. Because sAAA can be particularly difficult to diagnose, each documented case was retrospectively reassessed. Patients were regarded as sAAA in case the AAA symptoms had receded after treatment or if the symptoms could not be attributed to non-AAA pathology. The exact diameter for each patient was measured and documented in the hospital archives previous to this study as part of routine care. Ethical approval for the study was gained from the Institutional Review Board (METc2013-171). Informed consent was not required for this project.

AAA calcification measurements

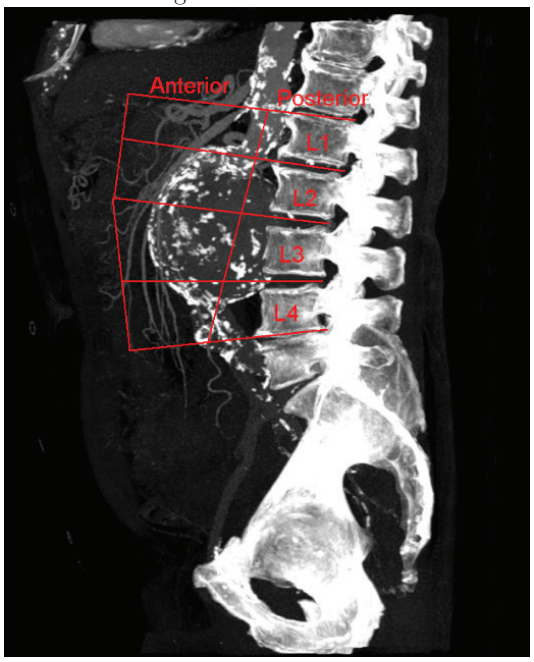
Independent radiologists confirmed the clinical diagnosis "AAA" for both the eAAA and non-eAAA groups. For analysis of CT images the AquariusNet Viewer Client V4.4.4.23 (TeraRecon, Foster City, California, USA) was used. To reliably image all calcifications in the three-dimensional (3-D) plane, a maximum intensity projection (MIP) was created from a sagittal perspective. The window level of each image was first adjusted in the AquariusNet Viewer Client. Iodine-contrast signal intensity has lower Hounsfield units (HU) than calcification. Therefore, by increasing the window level so that the iodine-contrast signal intensity becomes barely visible, calcification remains highly visible and no calcification signal is lost.Calcification in the AAA wall was later measured semi-quantitatively using the abdominal aortic calcium score (AAC-8) as described in earlier studies [18-19]. This is a simplified version of the AAC-24 score developed by Kauppila et al. [20]. The severity of calcification is measured

in points. These points are assigned to the presence of very high-density signals on the anterior and posterior walls of the abdominal aorta between the first and fourth lumbar vertebra. Therefore, one grade is given for the presence of calcification in the abdominal aorta alongside one vertebra on either the anterior or posterior side. If the calcification has an aggregate length of more than one vertebra, the grade increases one point and so forth. The cumulative points of both the anterior and posterior wall represent the AAC-8 score (Figs 1-3). Agreement for inter-rater reliability of the AAC-8 score was good (Kappa = .69; $P < .001$).

Figure 1. A sagittal MIP image from a thoracic CT scan in an AAA patient with abundant calcified structures.

Figure 2. A sagittal MIP image from a thoracic CT scan in an AAA patient with few calcified structures.

Figure 3. A sagittal MIP image from a thoracic CT scan in an AAA patient with a visualization of the measurement protocol according to the AAC-8 score.



Each lumbar vertebra up until number four has been numbered. A crude midline is drawn to show the anterior and posterior side of the AAA. The calcifications alongside the most ventral and dorsal wall are counted as either present or absent.

Statistical analysis

In addition to the separate statistical analysis of each group, sAAA and rAAA patient groups were also combined and labeled as non-eAAA. The distribution of calcification scores in groups with low-risk (≤50mm or ≤55mm for female and male patients, respectively) versus high-risk aneurysm (>50mm or >55mm for female and male patients, respectively) were also analyzed. Demographic statistics were expressed as mean ± standard deviation; 95% confidence interval (CI) (SD) for continuous variables for eAAA versus non-eAAA, respectively. Percentages were given for nominal variables and medians and interquartile ranges for skewed distributed variables. The demographic variables of non-eAAA patients and eAAA patients were compared. Cross tabulation was used to compare nominal variables. Continuous data were analysed using Student's T-test in case of normal distribution. Mann-Whitney U tests were performed for comparison of skewed continuous variables. Multivariate analysis was performed for the association between the patient groups (eAAA vs. non-eAAA) as the dependent variable and explanatory variables such as AAC-8 score and demographic variables. Logistic regression, using the backward conditional method, provided the predictive value of several explanatory variables. Inter-rater reliability was measured using weighted Kappa after cross tabulation of measurements by the main researcher and an experienced trained observer. Significance was set at $p \leq .05$. All statistical analyses were performed using SPSS 20 (IBM, Armonk, NY) except for the inter-rater reliability, for which STATA 11.2 (StataCorp LP, College Station, TX) was used.

RESULTS

Patient characteristics

Patients who had never smoked were more often found in the non-eAAA group (P = .013). All eAAA patients received treatment whereas 9% of non-eAAA patients did not receive surgery, either due to preoperative death, refusal of, or contra-indication to intervention. Treatment of eAAA patients was significantly more often by endovascular repair(P < .001) whereas non-eAAA patients received open repair more frequently (P = .003) (Table 1). Patients with PAD were significantly overrepresented in the eAAA group (21%) as opposed to only 8% in the non-eAAA group (P = .004). Age, serum creatinine, body mass index, current smoking habit, a history of cardiovascular disease, having stopped smoking, systolic blood pressure, diastolic blood pressure and mean arterial pressure either varied slightly, insignificantly or both between the groups eAAA and non-eAAA (Table 1). The frequency of COPD, hypertension and familial AAA incidence were also distributed equally over the two groups.

AAA diameter versus calcification

Aneurysm size differed strongly between eAAA and non-eAAA patients (62 ± 12 mm vs. 77 ± 20 mm; P < .001). Patients with eAAAs had a mean AAC-8 score of 3.4 ± 2 points, whilst rAAA patients had a score of 4.9 ± 2.2 points (P < .001). Between sAAA and rAAA patients, the difference was smaller and no longer significant (5.1 ± 2.3 points vs. 4.8 ± 2.2 points; P = .55). For the eAAA, sAAA and rAAA groups the AAA diameter measurements and AAC-8 score were plotted in an error bar (Fig. 4). The mean AAA diameter was highest in the rAAA group (79 mm; 74-83 95%-CI, followed by the sAAA group (72 mm; 63-82 95%-CI). The AAA diameter was lowest in eAAA patients.

Table 1. Distribution of demographic and clinical variables (eAAA versus non-eAAA).

Variable	Elective AAA (n= 230)	Non-elective AAA (n= 91)	P
Age (y)	70 ± 7.7	72 ± 8.2	.25
Serum creatinine (mg/dL)	101 ± 56	109 ± 39	.17
Blood pressure (mmHg)			
Systolic	137 ± 22	138 ± 25	.8
Diastolic	78 ± 12	77 ± 14	.71
Mean Arterial Pressure	98 ± 14	98 ± 17	.94
Body Mass Index	27 ± 4	27 ± 4	.82
AAC-8 (points)	3.4 ± 2.3	4.9 ± 2.2	< .001
AAA diameter (mm)	62 ± 12	77 ± 20	< .001
Diabetes mellitus (%)	16	21	.31
Hypertension (%)	61	64	.63
Cardiovascular disease (%)	73	64	.1
Peripheral artery disease (%)	21	8	.004
AAA in family history (%)	3	4	.54
Other aneurysms (%)	9	6	.28
Deceased (%)	10	13	.48
Smoking			
Never (%)	32	46	.013
Stopped (%)	26	18	.11
Current (%)	42	36	.30
Treatment			
Endovascular (%)	56	29	< .001
Open (%)	44	63	.003
No surgery (%)	0	9	< .001
Male gender (%)	93	92	.96
Chronic obstructive pulmonary disorder(%)	27	24	.67

Patient characteristics, measured data and common risk factors. Elective AAA patients were compared to non-elective AAA patients (Mean ± SD).

AAC-8: Abdominal Aortic Calcification 8 score

The AAC-8 scores were highest for sAAA patients. Patients with rAAA had the next highest AAC-8 scores. Patients with eAAA had the lowest mean AAC-8 score (Fig. 5). The combined predictive value of calcification and diameter are seen in Table 2. The distribution of patients with high-risk diameters and high calcification scores was significantly more pronounced in non-eAAA (55%) as opposed to eAAA patients (29%; $P < 0.001$). Patients who only had high calcification scores and small diameters comprised only 3% of the eAAA group versus 6% in the non-eAAA group, though this difference was not significant ($P = 0.2$). Large diameters with low calcification scores were seen significantly more frequent in eAAA patients (63%) compared with non-eAAA patients (40%; $P < 0.001$). Finally, there were no differences in the degree of calcification when patients were segregated into 2 groups according to aortic diameter (Fig. 6).

Figure 4. 95% confidence interval of the mean bar graph of AAA diameter size for elective, ruptured and symptomatic AAAs.

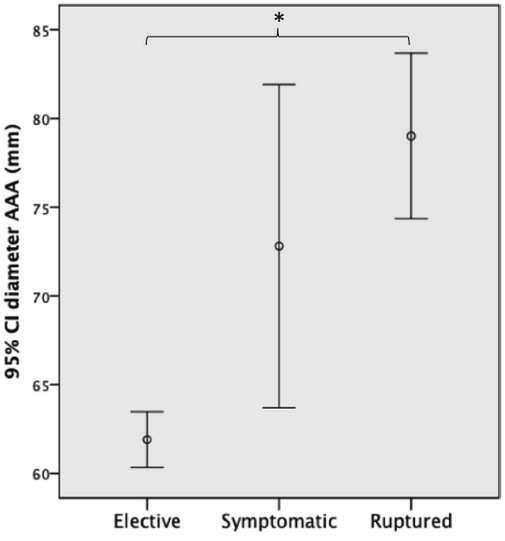


Table 2. Predictive value of calcification and diameter scores; combined and individual.

Variable	Elective AAA (n= 230)	Non-elective AAA (n= 91)	P
AAC-8 score > 4 and high-risk diameter (%)	29	55	< .001
AAC-8 score > 4 and low-risk diameter (%)	3	6	.2
AAC-8 score ≤ 4 and high-risk diameter (%)	63	40	< .001
AAC-8 score ≤ 4 and low-risk diameter (%)	6	0	.021

Distribution of four potential combinations of calcification grade and diameter size. High-risk diameter: >50 mm for female patients and >55 mm for male patients. *AAC-8: Abdominal Aortic Calcification 8 score*

Figure 5. 95% confidence interval of the mean bar graph of the AAC-8 score for elective, ruptured and symptomatic AAAs.

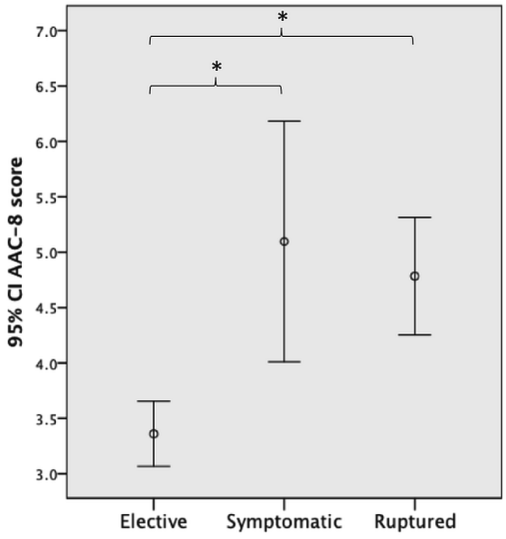
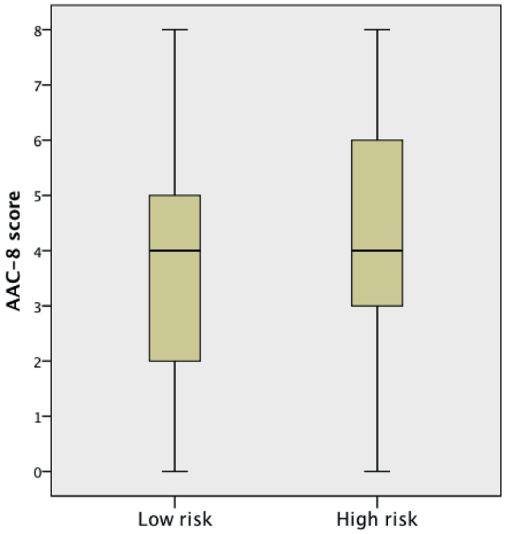


Figure 6. Box plot of AAC-8 score distribution in a low-risk diameter and a high-risk diameter group.



High-risk diameter: >50 mm for female patients and >55 mm for male patients.

Regression analysis

Correlation coefficients were first calculated in the eAAA and non-eAAA patient groups. Variables that maintained significance after logistic regression were AAA diameter, AAC-8 score, non-smoking, and history of PAD (Table 3). Patients with concomitant PAD were more often placed in the non-eAAA group with an odds ratio (OR) of .39 (95%-CI: .15 - 1; P = .049). The AAA diameter had an OR of 1.062 (95%-CI: 1.042 - 1.082; P < .001) for each mm increase compared to an OR of 1.35 (95%-CI: .15 - 1; P < .001) each point increase of the AAC-8 score.

Table 3. Results of multivariate analysis of eAAA versus non-eAAA.

Variable	P	Odds ratio	95% CI
AAC-8 (points)	< .001	1.35	1.19 - 1.53
AAA diameter (mm)	< .001	1.062	1.042 - 1.082
Smoking (never) (%)	.15	1.54	.86 - 2.76
Peripheral artery disease (%)	.049	.39	.15 – 1

Odds ratios for risk factors for rupture in elective AAA vs. non-elective AAA. AAC-8: Abdominal Aortic Calcification 8 score

DISCUSSION

In this study we assessed the correlation of calcification with aneurysm rupture risk. The amount of calcification in the abdominal aortic wall was higher in ruptured and symptomatic patients in contrast to electively operated AAA patients. However, possible confounding factors appeared to be unequally distributed over the different groups. Patients with a history of PAD were mostly found in the eAAA group. Also, a fair number of patients did not undergo or chose not to receive surgery in the rAAA group while all sAAA and eAAA patients did receive surgery. This phenomenon is understandable given the fact that the rAAA patient group has the largest preoperative mortality rate. Other potential confounders were either evenly distributed over the patient groups or showed very slight variation. The distribution of calcification scores in small versus high-risk diameter groups also showed that calcification scores were similar in both groups. Therefore, there does not seem to be major dependence of calcification score on aneurysm diameter. Nevertheless, when comparing the added predictive value of either calcification to diameter or vice versa, it is clear that a combination of >50% calcification and high-risk diameter size is more pronounced in the non-eAAA group. In comparison with the AAA diameter, the AAC-8 score was higher in sAAA than it was in eAAA patients. Most importantly, higher rates of both calcification and AAA diameter were found in the non-eAAA group as opposed to the eAAA group. We therefore state that calcification has value not only as an addendum to diameter but could also be associated with the development of symptoms in AAA patients. From the multivariate analysis between eAAA and non-eAAA patients, we can derive that an increase of either the AAC-8 score or AAA diameter are predictive of rupture and/or development of symptoms. To our knowledge, no previous studies have investigated the value of calcification in elective versus non-elective AAA patients. Some researchers however, have provided basic research and computational data that support our findings. Li et al. [10] performed a computational study in which CTA images of twenty patients were reconstructed as a digital 3-D model. The authors concluded that a causal relationship exists between calcification and significantly higher local wall stress. This, in turn, can decrease the AAA wall stability and consequently increase the risk of rupture. New et al. [11] described biochemical analyses of calcified AAA and stated that micro-calcifications of the AAA entail inflammatory cytokines, while macrocalcification plaques are more stable. Calcification would subsequently

deteriorate the structural integrity of the wall. Both Li et al. [10] and New et al. [11] provided a pathophysiological basis for our findings. Recently, Dweck et al. [21] were able to perform a functional analysis of the coronary arteries with 18F-sodium fluoride PET-CT. In their study they perceived a clear rise in cardiovascular risk in correlation with the activity of micro-calcifications. Though CTA is not capable of discriminating between active and inactive calcification, it may provide a clinically applicable tool in distinguishing micro- from macro-calcifications. The AAC-8 score is not suited to reliably differentiate between these two forms of calcification. The development of a quantitative calcification measurement tool could provide a widely applicable method to estimate the pathophysiological processes described above. Therefore, we plan to further study the influence of calcification on these processes and vice versa. A study by Lindholt [22] showed conflicting results. In this study, survival curves for mortality and cardiovascular events showed no significant differences in AAA with more than 50% versus less than 50% circumferential vessel calcification. On the other hand, a lower rate of expansion and decreased admission for surgery was observed for the group with over 50% calcification. These potentially protective effects might oppose the previous findings as well as the results presented here. The potential differences of the influence of macro- and micro-calcifications were not addressed in this study. Besides, the author stated that the reproducibility of the observations is uncertain. The AAC-8 score applied in our study does not account for circumferential calcification. It allows for measurement in the sagittal plane and might therefore not be directly extrapolated to the results found by Lindholt [23].

This study utilises the AAC-8 score, a method that has been used and validated in X-ray studies [16,23]. Before the AAC-8 score was introduced, Agatston et al. [24] had already constructed a computational method that could translate signal intensity as a function of Hounsfield Units (HU) into a quantifiable degree of calcification in coronary arteries. Callister et al. [25] validated a similar method, also based on HU, to calculate the total calcified volume. The strength of the AAC-8 score over the Agatston or Callister methods is its practicality in the clinical setting. Both the Agatston and Callister methods can only interpret calcification in non-contrast CT images. However, in the Netherlands the pre-operative anatomical assessment of the AAA is performed solely with CT angiography. Therefore, the Agatston and Callister methods currently

have no clinical value as opposed to the AAC-8 score. If a more accurate method of calcification measurement were to be applied in routine clinical practice, this could be used to validate the role of calcification in large groups of patients. Development of software tools applicable to CT angiograms will prove to be critical to enable such widespread use of calcification scores.

There are several limitations of this study. First, it should be underscored that the data for this study were collected retrospectively. Selection bias and confounding by known and unknown factors are the bane of retrospective studies. We have attempted to minimize selection bias in our population by including all patients whose CT images were available. Patients treated before 2005 were less likely to have available CT images as opposed to patients from 2005 forwards. We have included and assessed many of the possible confounders that have been identified in the current medical literature to minimize confounding. Naturally, other limitations apply to prospective research, though follow-up studies in a prospective manner would certainly be needed to substantiate our results.The AAC-8 score remains highly observer-dependent. A fully computational, observer-independent method will provide better reproducibility and validity. There is currently no such method for contrast-enhanced and unenhanced CT images. Still, inter-rater reliability in this study was good, confirming at least that the AAC-8 score is a fairly reproducible method. Though this study has promising results considering the relation between calcification and rupture, still very little can be said about causality. Further basic research on the interactions between calcification and aneurysm forming is needed to place the results of this study in perspective.

We found a trend of increased abdominal aortic calcification in patients with ruptured and symptomatic AAA as opposed to those undergoing elective repair. The maximum aortic diameter correlated well with symptomatology and rupture as expected. The AAC-8 score, but not AAA diameter, appeared to discriminate the group with symptomatic aneurysms from those undergoing elective repair. The results of this study suggest that calcification of the abdominal aorta might have predictive value. Additional research regarding the effects of calcification on vessel structure is needed to clarify the relation between calcification and rupture. Finally, this study shows a clear association of increased aortic calcification with aneurysm rupture.

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3.2

Quantification of abdominal aortic calcification: inherent measurement errors in current computed tomography imaging

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(PLoS One 2018;13:e0193419)

ABSTRACT

Objective: Quantification software for coronary calcification is often used to measure abdominal aortic calcification on computed tomography (CT) images. However, there is no evidence substantiating the reliability and accuracy of these tools in this setting. Differences in coronary and abdominal CT acquisition and presence of intravascular contrast may affect the results of these tools. Therefore, this study investigates the effects of CT acquisition parameters and iodine contrast on automated quantification of aortic calcium on CT.

Methods: Calcium scores, provided in volume and mass, were assessed by automated calcium quantification software on CT scans. First, differences in calcium scores between the abdominal and coronary CT scanning protocols were assessed by imaging a thorax phantom containing calcifications of 9 metrical variations. Second, aortic calcification was quantified in 50 unenhanced and contrast-enhanced clinical abdominal CT scans at a calcification threshold of 299 Hounsfield Units (HU). Also, the lowest possible HU threshold for calcifications was calculated per individual patient and compared to a 130 HU threshold between contrast-enhanced and unenhanced CT images, respectively.

Results: No significant differences in volume and mass scores between the abdominal and the coronary CT protocol were found. However, volume and mass of all calcifications were overestimated compared to the physical volume and mass (volume range: 0-649%; mass range: 0-2619%). In comparing unenhanced versus contrast-enhanced CT images showed significant volume differences for both thresholds, as well as for mass differences for the 130 vs patient-specific threshold (230 ± 22.6 HU).

Conclusion: Calcification scoring on CT angiography tends to grossly overestimate volume and mass suggesting a low accuracy and reliability. These are reduced further by interference of intravascular contrast. Future studies applying calcium quantification tools on CT angiography imaging should acknowledge these issues and apply corrective measures to ensure the validity of their outcomes.

INTRODUCTION

Much like calcification of the coronary wall, abdominal aortic calcification has garnered interest for becoming an important independent risk factor for cardiovascular health [1-4]. Since vascular calcification is a proxy measure for a prolonged disease state of the medial or intimal wall, it seems reasonable to investigate clinical outcomes based on calcification measurements [5-6]. It is a diagnostic feature, most often visualized with computed tomography (CT) scanning. Additionally, it has been associated with other endpoints as well, such as renal disease, non-alcoholic fatty liver disease and colorectal anastomotic leakage [7-9]. The conclusions of these studies are directly linked to the reliability of the method of measuring the extent of aortic calcification. However, there is no scientific evidence substantiating the accuracy and reliable use of currently available automated measurement methods for aortic calcification. As many of the aortic calcification measurement methods are based on studies performed on coronary arteries, the assumption of equal accuracy and reliability with aortic measurements may be unfounded. There are important differences that should be accounted for, such as vessel size and wall thickness, hemodynamics and the presence of different surrounding organs. The use of intravenous contrast, which is commonplace in abdominal CT imaging, contributes also to difficulties in measuring calcification. The presence of contrast can overshadow calcified structures of similar or lower radiopacity and therefore interfere with the reliable measurement of calcified entities [10]. The scoring tools for coronary artery calcifications should only be applied on CT scans obtained with a coronary CT protocol or equivalent type protocols, without the use of intravenous contrast [11]. This study was performed to assess the effects of CT acquisition parameters and iodine contrast on the measurements of aortic calcification on CT images. The results provide new insights on the low reliability of calcium quantification on CT, under these different circumstances.

METHODS

Study design

To evaluate the influence of CT acquisition parameters and iodine contrast on the quantification of aortic calcification, this study was split in two parts. Part one consisted

of multiple CT scans of a validated thoracic phantom under two scanning protocols, coronary and abdominal. As the phantom contains calcium elements with known mass and volume, this part allows for the evaluation of the effects of scanning protocols on calcium quantification results. Part two of this study focuses on the quantification of calcified vessel elements in unenhanced versus contrast-enhanced, retrospectively collected, clinical abdominal CT scans. The Institutional Ethical Review Board (METc 201600621) waived the requirement for informed consent and approved this study. All data were anonymized after collection.

Phantom data acquisition

Two standardized and clinical protocols for the coronary arteries and the abdominal aorta, respectively, were compared in a phantom study. A validated thorax phantom (Fig. 1A, QRM-Thorax, QRM GmbH, Moehrendorf, Germany) was used for coronary calcification scoring. The phantom consists of an anthropomorphic thorax of tissue equivalent material with a removable cardiac calcification insert [12-14]. The insert contained nine cylindrical elements (Fig. 1B) organized in three series of different calcium hydroxyapatite densities and sizes (Table 1). All CT images were acquired using a 64-slice CT-scanner (Siemens Somatom Sensation, Siemens Healthcare GmbH, Erlangen, Germany). The phantom was scanned with both a standardized coronary artery and an abdominal aorta protocol (Table 2). Both protocols were identical to the institutional standard for clinical care. Five CT scans of the phantom were made with both protocols. Between each CT scan the phantom was moved 2-5 mm in a random direction to mimic patient movement.

Calcification quantification software

3Mensio structural heart version 6.0 (3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) was used to calculate calcium volume and mass. 3Mensio was built with the intent to not only quantify coronary calcification, but aortic calcification as well. However, the software was only validated for the quantification of coronary calcification [12]. Calcium volume and mass were calculated using a standard threshold of 130 HU [15]. Calcium volume and mass of the small, medium and large calcifications were compared between the coronary and abdominal CT protocols and to the physical volume and mass.

Figure 1A. The anthropomorphic thorax phantom. (Reference image provided by QRM GmbH).

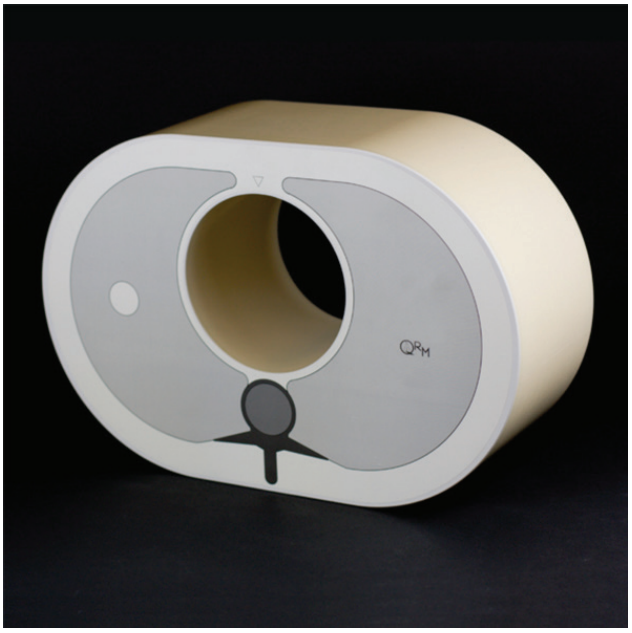
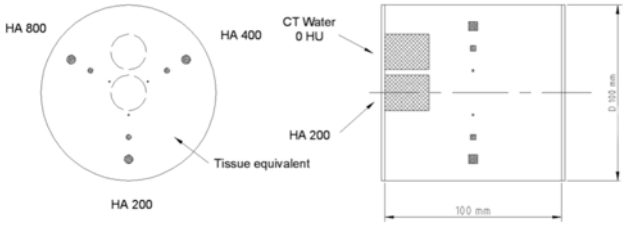


Figure 1B. Frontal (left) and sagittal (right) view of the cardiac calcification insert.



It contains nine cylindrical calcifications with different masses and volumes, as well as one large water equivalent element and one large calcium hydroxyapatite calibration element. (Reference image provided by QRM GmbH).

Table 1. Cardiac calcification inserts characteristics.

Spot	Volume (mm^3)	Mass (mg)	Density (mg/cm^3)	Diameter (mm)
1	0.8	0.16	200	1
2	21.2	4.2	200	3
3	98.2	19.6	200	5
4	0.8	0.32	400	1
5	21.2	8.5	400	3
6	98.2	39.3	400	5
7	0.8	0.64	800	1
8	21.2	17.0	800	3
9	98.2	78.6	800	5

kVp: Kilovoltage peak
mAs: milli Ampere seconds
Field of view: Acquisition field of view

Table 2. CT protocol characteristics.

CT protocol	kVp	Effective mAs	Slice thickness (mm)	Collimation (mm)	Convolution kernel	Field of view (mm)	Reconstruction matrix (mm)
Coronary	120	190	2.0	0.6 – 0.8	b35f	300	512 x 512
Abdominal	120	23-26	2.0	0.6 – 0.8	b30f	300	512 x 512

kVp: Kilovoltage peak
mAs: milli Ampere seconds
Field of view: Acquisition field of view

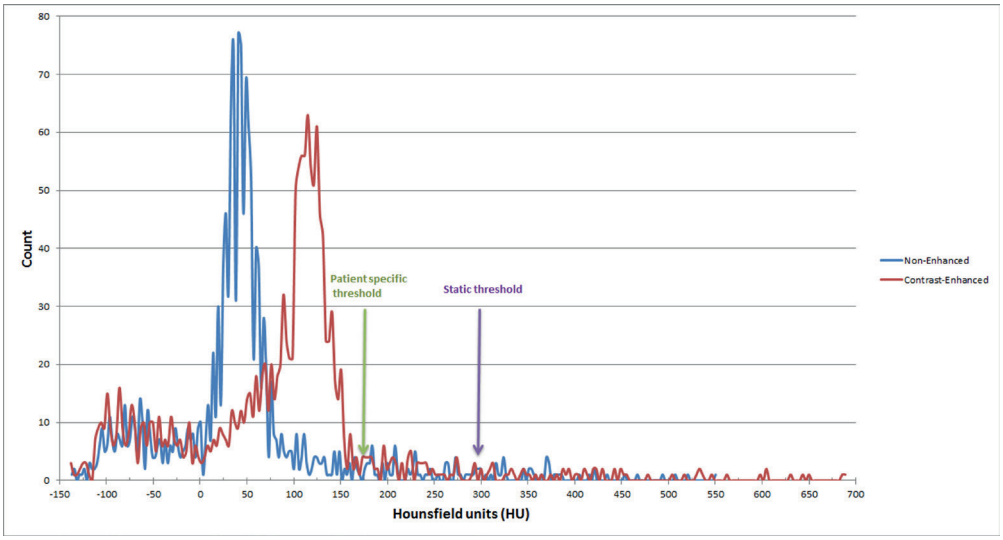
Unenhanced versus contrast enhanced CT images

To assess the effects of CT iodine contrast on the measurements of aortic calcification, both contrast-enhanced and non-enhanced CT images of the same patients that contained a sufficient length of the abdominal aorta were required. Four-phase liver CT scans allow for these scans to take place in quick succession and were readily available, since these had already been performed as part of routine clinical care. Tri- and bi-phasic liver CT scans were found to a significantly smaller degree. Thus, for the purpose of standardization, only four-phase liver CT scans were included.

Consequently, 50 clinical four-phase liver CT scans were retrospectively collected and analysed from all four-phase liver CT scans that were conducted between 2013 – 2015. The following inclusion criteria were applied to minimize selection bias, whilst maintaining a technically qualitative and representative sample of clinical patients with abundant aortic calcification to quantify. Patients over 65 years of age were included by non-stratified simple random sampling, regardless of the clinical indications or results of the four-phase liver CT scan. Clinical patient endpoints were not collected, as these were not deemed relevant to addressing the main goal of the study. Only patients with complete scan information and data were included. Also, inclusion required a b30f reconstruction kernel at an increment of 2.0 mm. From the four-phase liver CT scans, the first unenhanced scan was used as well as the second contrast-enhanced arterial phase scan. As clinical CT angiography of the abdominal aorta only requires one contrast-enhanced scan, the third (venous) and fourth (late) phase acquisition was not deemed relevant to this study.

All scans were acquired as part of standard patient care on a Siemens Somatom Sensation 64-slice MDCT-scanner. The collimation slightly differed per patient from 0.6 x 0.6 to 0.8 x 0.8 mm. All arterial phase images were reconstructed to a slice thickness of 2.0 mm, as increasing the slice thickness to the generally applied 3.0 mm would also increase variability in calcification scores [16]. Regions-of-interest were selected on a case-by-case basis for both the unenhanced and the contrast enhanced phase in the abdominal aorta segment found between L1 to L4. In the contrast-enhanced scans, a patient-specific threshold in Hounsfield Units was used to ensure a clear discrimination between contrast and calcifications. This threshold was calculated according to the global thresholding principle (Fig. 2). To compare non-enhanced scans and enhanced scans with a similar threshold, a fixed threshold was calculated as well that includes as much calcification signal as possible whilst minimizing contrast signal. This threshold is based on the mean + three standard deviations of the patient-specific threshold. This ensures correct distinction of luminal contrast and calcifications in all scans with calcification signal intensity (Hounsfield Units) within three standard deviations of the mean.

Figure 2. Histogram of the HU levels of the non-enhanced and contrast-enhanced CT scans of one patient.



The arrows show the selected thresholds. Purple arrow: static threshold (299 HU). Green arrow: patient specific threshold.
HU: Hounsfield Units

Statistical analysis

The primary endpoints, in case of non-normal distribution, were reported as summed volumes or mass and their median + range. For normally distributed data, the mean ± SD were provided. Comparisons between protocols were performed using Mann-Whitney U tests. The correlation between calcium scores of non-enhanced and enhanced scans were assessed using related-samples Wilcoxon Signed Rank tests with concordance testing using related-samples Kendall's coefficient of concordance. Correction for significance was performed according to the Bonferroni method. A post-hoc power analysis was performed for the Wilcoxon Signed Rank tests of the non-enhanced and contrast-enhanced CT scans [17]. No post-hoc power analysis could be performed for the phantom study since Mann-Whitney U tests do not provide z-values, which are necessary to estimate effect sizes for non-normally distributed data. SPSS 20 (Statistical Package for the Social Sciences, IBM, Armonk, NY, USA) was applied for statistical analyses. All data underlying the results of this study were made available for reference.

RESULTS

Phantom data results

Results for calcium volume and mass in the coronary and abdominal scanning protocols were compared and tabulated in Table 3. The measurements of the smallest and medium sized calcium cylinder were higher for the abdominal protocol than for the coronary protocol (+2.5% (-100 – 649) versus -45% (-100 – 388)), although not significant. The mass measurements of the smallest and medium cylinder were higher, yet not significantly, for the abdominal protocol than for the coronary protocol (+313% (0 – 2619) versus +131% (0 – 1563)). Despite the non-significant differences, all measured calcium volumes varied greatly from the true values with the maximum differences ranging up to +649%. For calcium mass measurements the same was true, except for even greater variation of up to +2619%.

Table 3. Percentual differences of the measured volume and mass of the small cylinder, medium-sized and large cylinder with respect to the physical volume and mass in a coronary and abdominal CT protocol.

		Small cylinder difference (%)	Medium cylinder difference (%)	Large cylinder difference (%)
Volume	Coronary	-45 (0 – 388)	+66 (98 – 278)	+56 (104 – 220)
	Abdominal	+2.5 (0 – 649)	+83 (113 -264)	+54 (112 – 192)
Mass	Coronary	+131 (0 – 1563)	+576 (400 – 1136)	+58 (105 – 221)
	Abdominal	+313 (0 – 2619)	+648 (462 – 1076)	+55 (113 – 193)

Non-enhanced versus contrast-enhanced CT images

The fixed threshold for this population was calculated to be 299 HU. The mean patient-specific thresholds were 230 ± 22.6 HU. The mean calcium mass and volume measurements, based on the 130 HU threshold, 299 HU threshold and patient-specific threshold, are found in Table 4. The differences between the unenhanced and the contrast-enhanced calcification scores were tabulated here as well. Calcification volume (2421 [16.4 – 13882] versus 1358 [15.5 – 12798], $p < 0.001$) and mass (647 [2.9 – 6073] versus 583 [5 – 6630], $p < 0.001$) measurements were significantly higher for non-enhanced scans in case the 130 HU threshold was compared to the

patient-specific threshold. However, in case the fixed threshold was used, the results were higher for contrast-enhanced scans and significantly so for volume measurements (875 [0 – 9013] versus 1001 [1 – 11091], $p < 0.001$). This outlier was found in case calcium mass was measured with the 299 HU threshold in both the unenhanced and the contrast-enhanced scans (442 (0 – 5251) versus 480 (0.3 – 6247), respectively). In accordance with the Bonferroni-adjusted significance level of 0,0125, the difference can no longer be considered significant. Since multiple analyses were performed, the effect size measured in this study ranged between 0.2341 and 0.5536, resulting in an overall power of 0.61 to 0.99.

Table 4. Results of non-enhanced versus contrast-enhanced CT scans

	Threshold (HU)	Non-enhanced (median (range))	Contrast-enhanced (median (range))	Difference (median (range))	Wilcoxon signed rank (p-value)	Kendall's coefficient of concordance (p-value)
Volume (ml)	130 vs pat-spec	2421 (16.4 – 13882)	1358 (15.5 - 12798)	998.8 (-4665 – 5280)	<.0001	<.0001
	299 vs 299	875 (0 – 9013)	1001 (1 – 11091)	-78.95 (-7217 – 201)	<.0001	0.02
Mass (mg)	130 vs pat-spec	647 (2.9 – 6073)	583 (5 – 6630)	90.7 (-3973 – 870)	<.0001	<.0001
	299 vs 299	442 (0 – 5251)	480 (0.3 – 6247)	-11.35 (-4263 – 443)	0.019	0.024

HU: Hounsfield Units
Pat-spec: patient-specific threshold
Non-enhanced: data of non-enhanced liver CT scans.
Contrast-enhanced: data of contrast-enhanced sliver CT scans.
Difference: difference between non-enhanced and contrast-enhanced CT scans.

DISCUSSION

This study set out to investigate the effect of technical changes on the measurements of aortic calcification on CT images. The combined results of this study's tests suggest that the current software technology for aortic calcification measurements of CT images is unreliable. This is due to several important restrictions. These are as follows: 1. The size of the calcification is inversely correlated to the degree of the measurement error; 2. Direct application of software developed for coronary calcification measurements to the abdominal aorta provides grossly erroneous and more importantly, highly variable outcomes; 3. Applying automated calcification measurement software under clinical conditions, i.e. in the presence of intravascular contrast, further disrupts the accuracy of the measurements. The gross overestimation and variability of the calcium measurements is largely caused by partial volume averaging. This is a common artefact in radiography, yet has very little significance in descriptive radiology, since the current generation of CT scanners provide an adequate resolution for visual investigation. Regrettably, voxel-by-voxel analysis by quantification tools, still suffer from partial volume averaging. In short, one voxel on a CT scan can currently contain multiple tissues, like a partial vessel wall, calcifications and blood. The radiodensity of each of these tissues are averaged, since one voxel can only give one HU signal. Few voxels are entirely filled up by small calcifications, yet these do increase the average HU of the surrounding tissues. That explains why smaller sized calcifications are more prone to erroneous measurements than larger ones. This, in turn, creates the illusion that its volume is greater than it in fact is, which is especially pronounced in the case of multiple small calcifications. Partial volume averaging should affect coronary and aortic CT scans equally, therefore its implications may be dismissed to a similar degree. Further detailed research on partial volume averaging in aortic calcification imaging should be performed to substantiate this dismissal. Also, partial volume averaging effects are circumvented to a significant degree in coronary quantification assessment through the application of a semi-quantitative analysis. No such method has been validated for assessing aortic calcification. Additionally, other differences to coronary artery calcification imaging should also be taken into account. For instance, introduction of high-density contrast will create HU signals that overlap with those of any calcified spots and overestimate the volume even further than the partial volume

averaging would. Allowing AAA patients to undergo an additional venous phase CT scan could potentially improve the results, and diminish this issue. However, this would entail additional radiation exposure, at least in centres where the arterial phase is deemed most relevant for imaging the aorta in AAA patients. Adequate thresholding and segmentation should minimize these overestimations, although to a limited extent. In fact, especially with threshold-dependent automated quantification tools, it is understandable that major differences in calcification measurements were found between unenhanced and contrast-enhanced CT scans in this study. By choosing the lower HU threshold, the user decides at which minimal HU level an entity on CT is a calcification or not. The 130 HU lower threshold was chosen for unenhanced scans, as it mimics the well-documented use of HU thresholds for coronary artery CT scanning [18]. However, as our results imply, in case intravascular contrast is imaged, this threshold will be too low, resulting in major overestimations of the calcium volume and mass. Therefore, once contrast is introduced, the lower HU threshold for calcification should be raised to correct for the contrast HU level. Since contrast-volume and dispersion of contrast in the patient-dependent volume of blood change between each time a measurement is performed and between each different patient, the threshold should also be patient- and event specific. Previous research by Komen et al. corroborates these results, as the authors compared calcification scores measured with ten different lower HU thresholds for calcification, ranging between 130 and 1000 HU. The authors found that it was not possible to reliably compare calcification scores between scans that were analysed based on different thresholds [10]. Additional research on the correct lower HU threshold for calcification in CT scans of the abdominal aorta is required before any further calcification quantification tools can be applied for predicting clinical outcomes. No measurement tool that has been applied in this field, nor those that are currently in development, are reliable as long as the tools depend on HU values and thresholding as a means of distinguishing between calcified and non-calcified tissues.

This study is first to discuss the technical and practical effects of differing CT scanning settings and the presence of intravascular contrast on aortic calcification scores on clinical CT images. This should be regarded as remarkable considering the studies that have been produced with a variety of presumed aortic calcification scoring tools [7-9, 19]. In these studies, important endpoints, renal health or diabetes, among many

others, were correlated to abdominal aortic calcification volume or mass. The studies referenced here are some of many, although an in-depth analysis of these papers would require a dedicated systematic review and meta-analysis. The abovementioned studies proposed correlations between the aortic calcification scores and the respective outcomes. It is therefore paramount that the accuracy of the applied techniques is tried and tested before many of these correlations can be reliably put forward. Especially in light of the questionable reliability of aortic calcification scoring software, as displayed by the wide ranges in this study. This study has several limitations. Firstly, no pre-test power analysis was performed, as no data was available for any suggestions of expected effect size. Therefore, especially the low amount of scans of the phantom study provides a low power. Nonetheless, despite the fact that no firm arguments ought to be made about the difference between the two scanning protocols, this does not negate the obvious discordance between the actual mass and volume, versus what was measured under highly controlled circumstances. Another point of contention could be the fact that the phantom applied in this study is not an abdominal aorta-specific phantom. Therefore, its applicability may be questioned.

There is currently no research experience with abdominal aorta phantoms. However, there are publications on the thorax phantom, specifically with regard to coronary calcification [15]. This at least suggests that applying the coronary CT scan protocol on the thorax phantom is reliable, even if the abdominal CT scan protocol is not. Also, this study employed a calcification measurement tool, which has not been clinically validated to reliably measure aortic calcification. This is, however, exactly the reason why this study was performed. Despite the lack of previous applications of the software, the tool did provide adjustability in measuring calcifications in the presence of contrast. Since these software tools work according to similar basic algorithms, the software is assumed to be representative in measuring aortic calcification. Previous research on aortic calcification quantification has generally been aimed at current technology applied in general clinical practice. Therefore, this study only focused on HU-dependent quantification software and 64-slice MDCT technology. However, it should be noted that quantification software packages that do not rely on Hounsfield Units might provide different results. The use of other CT modalities, such as electron beam or dual source CT, is also expected to provide different results to those

purported in this study. Lastly, as the patient body type can influence radiation dosage and Hounsfield Unit intensity, prospective collection of this information would have provided additional insights on its potential effects on calcification scores. Yet, as tube voltage and tube current are adjusted based on individual patient body type, these potential confounding effects on calcification scoring will have been minimized in this study.

CONCLUSION

Aortic calcification scoring on CT angiography currently suffers from several key issues. The main restriction is the gross, and more importantly, highly variable overestimation of volume and mass measurements. Second, the error increases for small calcium spots, such as those found in the clinical setting. Third, both these issues are worsened by the presence of intravascular contrast. Further research on the reliability of many automated calcification measurement tools ought to be performed before these are further implemented for research and clinical purposes. Experimental studies that rely on the accuracy of these tools without acknowledging the issues purported in this study, should be thoroughly scrutinized before further research is built upon their results.

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Chapter 4

Novel approaches in prognostics and prevention of type 1A endoleak

4.1

Prevention and management of type Ia endoleaks: EVAR versus EVAS

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(Vascular and endovascular challenges update. Greenhalgh RM (ed.). BIBA Publishing, BIBA Medical Ltd, London, 2016. pp. 341-348)

INTRODUCTION

Endovascular aneurysm repair (EVAR) has become the preferred treatment for abdominal aortic aneurysms (AAA) but the need for a reduction in re-intervention rate is ongoing. Endoleak is the major complication of EVAR and the main indication for re-interventions[1]. The EUROSTAR investigators found that endoleak is a predictor for conversion to open repair and secondary rupture. 41% of patients with endoleaks remained free from secondary interventions within the first two postoperative years as opposed to 91% in those without endoleaks[2]. Endoleaks are classified in five subtypes based on location and causative mechanics. Proximal endoleak, known as type Ia, is especially of interest as it is considered a high pressure endoleak and might have a surgeon and/or graft dependent incidence[3]. In 2013 Endovascular Sealing of Aneurysms (EVAS) using the Nellix® endoprothesis (Endologix Inc., Irvine, CA, USA) was introduced. Early results from the EVAS-IDE trial and an interim analysis of the EVAS Global Registry have shown a low overall endoleak rate, but when occurring most are type Ia endoleaks[4]. In the present chapter we will review literature on type Ia endoleaks after both EVAR and EVAS.

Type Ia endoleak after EVAR

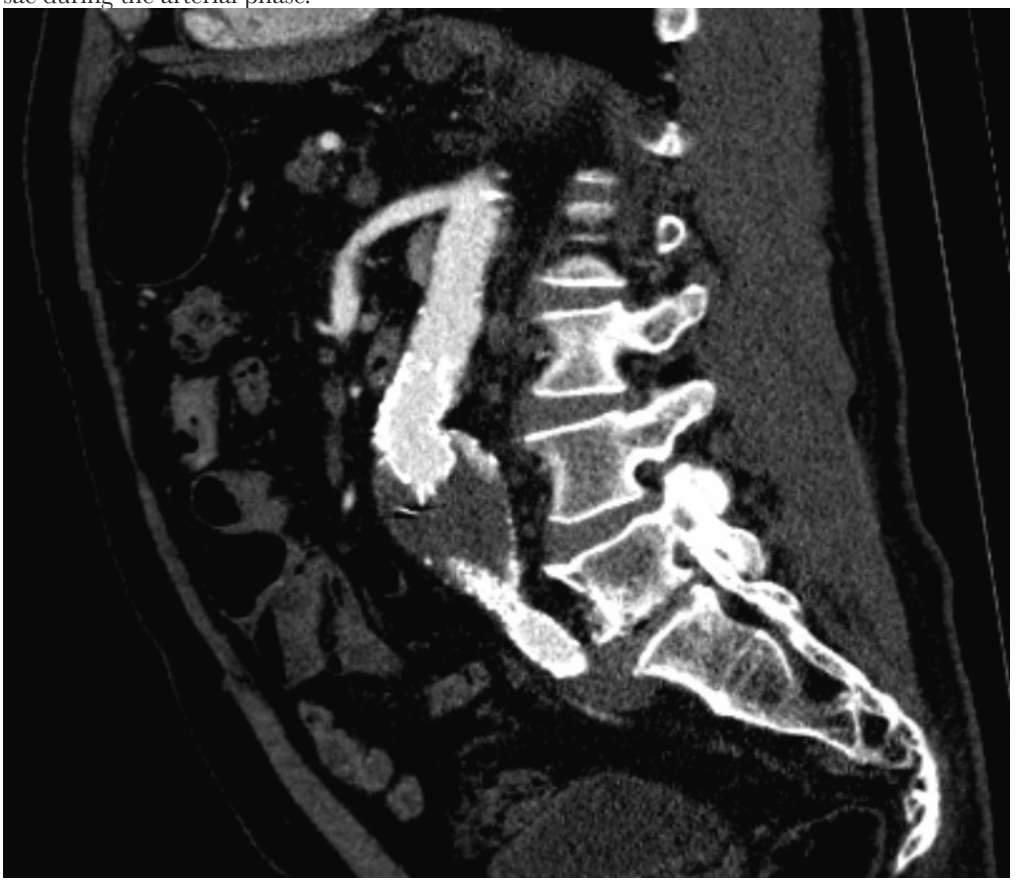
Endoleak is defined as persistent blood flow into the aneurysmal sac despite presumed AAA exclusion and can be observed both intra-operatively (Fig. 1) and during post-interventional surveillance. A type Ia endoleak shows contrast outside the proximal sealing zone of the endograft filling the aneurysmal lumen. Contrast-enhanced computed tomography angiography (CTA) imaging is considered the primary diagnostic (Fig. 2), although there is no true consensus[5]. Modalities as duplex ultrasound and MRA have their value in the diagnostic process, as have the newer options ECG-gated CT and MRA[6].

Type Ia endoleaks can be related to other endoleaks, specifically type II and V. Especially in combination with a growing AAA, a type II endoleak should be evaluated as a "type Ia in disguise", potentially explained by an intermittent inflow. Type V endoleak is a category for aneurysm growth of uncertain cause that could be the result of previous endoleak that perpetuates its tension on the aneurysm sac. Blackwood et

al. showed that type I endoleak sometimes results in no net inflow of contrast, despite the fact that the aneurysm sac expands. In the absence of net flow into the aneurysm sac, contrast cannot reach outside the endograft in high enough concentrations to visualize its presence[7]. The occurrence of a type Ia endoleak after EVAR can have various causes, including: 1. patient-specific variables, such as infrarenal aortic neck anatomy; 2. clinician-dependent variables, such as experience with sizing and endovascular technique, and compliance to the instructions for use; and 3. endograft-specific characteristics, such as suprarenal fixation and the presence of hooks or barbs. Early type Ia endoleak, occurring within 30 days after implantation, is often related to pre-operative planning, patient selection and/or technique while a late-type type Ia endoleak is more frequently caused by graft migration, infrarenal neck dilatation or kinking of the graft due to severe neck angulation[8].

Figure 1. Procedural type 1a endoleak after EVAR as appeared on completion angiography.

Figure 2. Type 1a endoleak on CTA with proximal contrast extravasation inside the aneurysm sac during the arterial phase.



Anatomic variations play a key role in the occurrence of type Ia endoleaks and the identification of hostile neck anatomy has led to a better understanding of requirements. This, in turn, has improved endograft design, like the development of endografts with an indication for severe angulation and repositionable endografts. Recently, Jordan et al. postulated a strong link between the occurrence of type Ia endoleak and the infrarenal neck length, neck diameter, and the presence of mural thrombus, while the other hostile neck characteristics seemed to be less important[9]. In recent years endografts have been developed to treat AAAs with a more hostile neck anatomy. The Anaconda™ endograft offers a repositionable deployment system and thus more accurate positioning and as such, potentially less type Ia endoleak. Similar to the Anaconda™ endograft, the Gore C3 Excluder system (WL Gore and Associates,

Flagstaff, AZ, USA) can be repositioned as well and has proven to succeed in several single center studies. In these studies, repositioning was applied in 49% of the cases, leading to just two type Ia endoleaks in follow up[10]. It can be difficult to distinguish whether type Ia endoleak is caused by anatomical factors, technical issues and/or sizing or by a combination of both. Experience is considered important but yet the effect of the clinician's skills has hardly been studied. Some studies have claimed that results were influenced by learning curve of the department or the clinician[11,12]. No comparative research has been performed on preoperative sizing techniques, despite the availability of potentially more accurate methods[13]. The overall incidence of type I endoleak seems to vary between 7.5 - 10.5%[14]. There is a lack of consensus in the outcomes of endoleak type Ia treatment and follow-up. A benign course was described by Millen et al. who found that only 2 of 44 type Ia endoleaks persisted beyond the first post-operative CT, following intraoperative treatment of the endoleaks and subsequent watchful waiting. On the other hand, larger studies have shown significantly worse outcomes. In a multicenter study on 2730 EVAR cases 22 post-EVAR ruptures were recorded and 73% of them presented in conjunction with a type Ia endoleak. Once type Ia endoleak is found, treatment is usually indicated and several techniques can be applied. When the proximal stent of the device is not fully expanded, an additional ballooning of the stent could complete seal. If unsuccessful, a proximal cuff could be introduced, although there should be adequate infrarenal aortic neck length for the cuff to land. This technique is chosen to treat a type Ia endoleak that is caused by either misplacement or late migration. Balloon expandable stents can be used in case of folding of the graft material or an incomplete expanded stent. In an eight-year follow-up study Rajani et al. showed a 6% recurrence of type Ia endoleak in cuff-treated patients, and nil in Palmaz stent treated patients[15]. In case of inadequate infrarenal neck length, a fenestrated cuff could be used (Fig. 3). A potential alternative is the a proximal cuff in combination with chimney grafts,. Chimney's, however, have been related to a high incidence of type Ia endoleak themselves[16]. As an adjunctive Endoanchors (Aptus Endosystems, Sunnyvale, CA, USA) can be used to fixate the initial stentgraft in case of distal migration and be combined with proximal cuff or can reduce inward folding of graft material (Fig. 4)[17].

Should these techniques fail the option of using embolizing agents to close the aneurysm sac opening remains. The introduction of coils and N-butyl cyanoacrylate have shown

promising results in the past, but lag behind in recanalization risk and ease of use. The Onyx system, an ethylene vinyl alcohol copolymer, showed excellent applicability in all EVAR devices, low risk of recanalization, good primary results and acceptable mid-term results up to two years. However, long term research is required, as the authors only studied the follow-up in one center and in eight type Ia endoleak patients[18].

Figure 3. Procedural angiographies of a patient with progressive neck dilation, distal migration and a minor type Ia endoleak repaired using a three-fenestrated cuff.

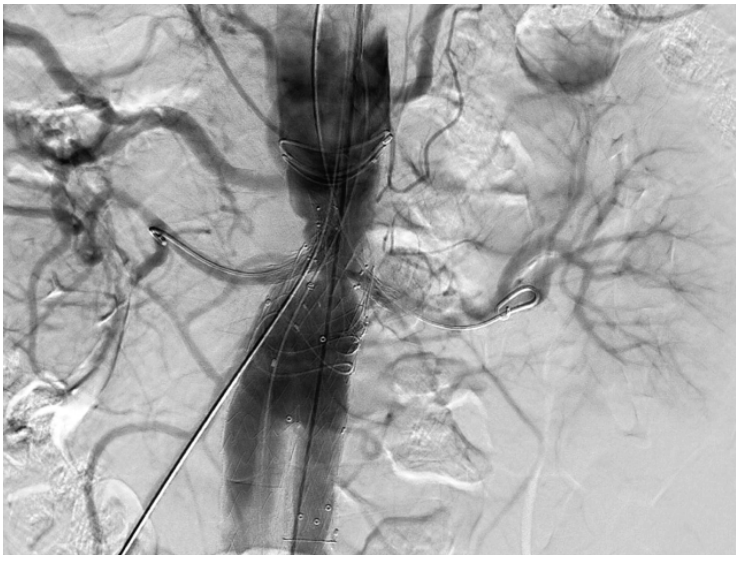
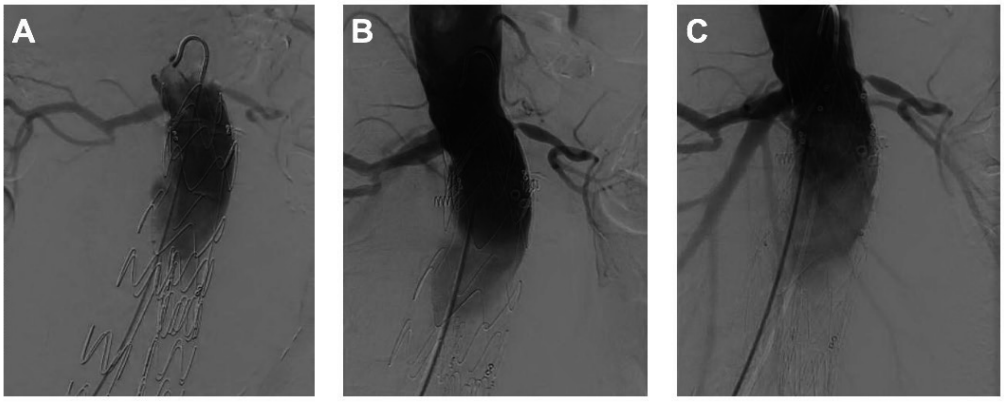


Figure 4. Type Ia endoleak on angiography caused by distal migration of the endograft (A) Aptus EndoAnchor implantation for fixation of the EVAR device (B) Additional proximal cuff placement in conjunction with Aptus EndoAnchors to seal the endoleak (C).



EndoVascular Aneurysm Sealing using the Nellix® endograft

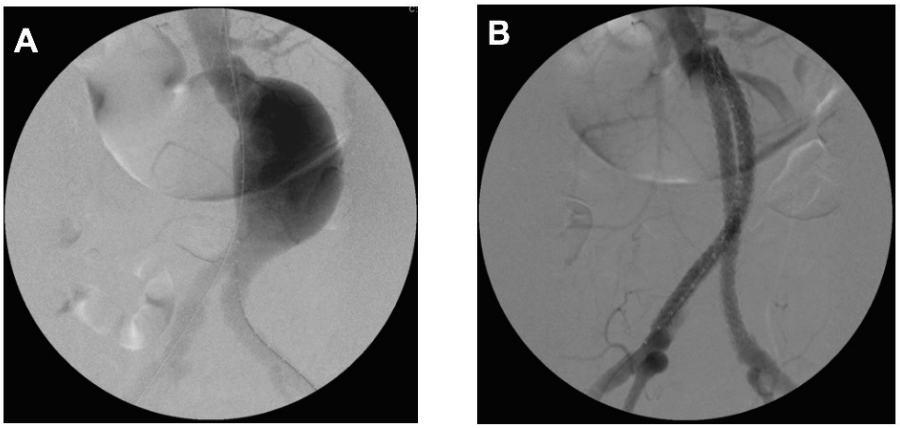
The Nellix® EndoVascular Aneurysm Sealing (EVAS) System (Endologix Inc., Irvine, CA, USA) was introduced in 2013 and the concept differs from EVAR, as endobags, surrounding the balloon expandable stents, are filled in situ with a biocompatible polymer for aneurysmal sealing. The polymer is injected in a liquid state and cures to a solid state at body temperature, thus conforming to the aneurysm shape. This provides stability and seal from the aneurysmal sack and anchoring the stents inside the aneurysm. These polymer-filled endobags reduce the space for endoleaks to occur and could broaden the applicability of treatment of aneurysms[19]. Procedurally, two Nellix® stents are expanded and the endobags are subsequently prefilled with a saline solution in order to expand the endobags, confirm the required filling volume, and to verify the absence of endoleak with the intended 180 mmHg pressure in the endobags. In case an endoleak occurs additional volume is added to increase the pressure by 20 mmHg, followed by a new angiography to confirm complete seal. Then the saline solution is replaced by the polymer. During polymer curing the Nellix® balloons are re-inflated to optimize the flow lumen. When indicated, secondary fill can be performed after removal of the safety wires and primary fill line. Lastly, final angiographies performed to confirm patency, absence of endoleak, and correct stent positioning.

The true incidence of type Ia endoleak after EVAS is unknown. The Nellix® System IDE Pivotal Trial included 150 patients [4]. The mean AAA diameter was 58 mm and all patients were within the instructions for use. Procedural success was 100% and at 30-days the core-lab identified nine endoleaks of which eight type II and one type Ia. The type Ia endoleak was associated with a procedural stent misalignment and was treated with coil embolization. In the EVAS-Global registry 300 patients were included in 30 sites. Patients were included without prospective screening and only 190 patients were within the IFU4. There were eight endoleaks within 30 days of which one type II, one type Ib and six type Ia endoleaks, all in the cohort within the IFU. Four reported endoleaks were treated successfully and two remained present at 30 days. The combined incidence of type Ia endoleak at 30-days after EVAS is 0.4% with an overall early incidence of 1.5%. During longer follow-up, four new type Ia endoleaks occurred that required secondary intervention. One patient suffered from a ruptured aneurysm related to a type Ia endoleak and received secondary open surgery.

Complaint data from the commercial use of Nellix® suggests that type Ia endoleaks occur more often during early experience, suggesting there is a learning curve. For those who reported a type Ia endoleak, the average number of cases until the reported first event was 4.9 cases. The reports of type Ia endoleak submitted within first ten cases was 85% and only 27% submitted more than one type Ia endoleak. Analysis of these endoleaks revealed they were mostly due to poor stent position and/or alignment. Type Ia endoleaks seem to occur more frequently with new users and new users appear to adapt to the learning curve quickly and improve their technique to eliminate future type Ia endoleaks. Data from this analysis as well as the EVAS global registry have therefore suggested that early type Ia endoleaks appear to be related to a learning curve.

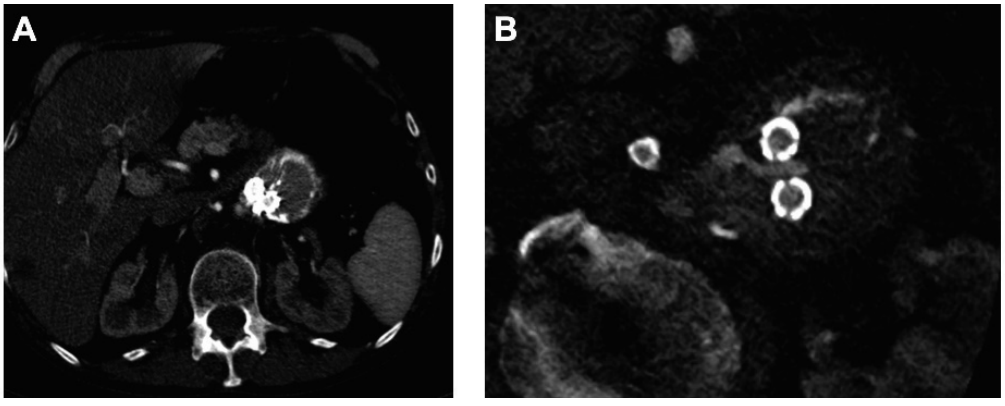
Causes of type Ia endoleak after EVAS include incorrect low placement of the endografts, an inadequate filling of the endobags and late migration. Several steps could improve outcome of the procedure. Patient selection is the starting point in preventing type Ia endoleak equal to EVAR. Asymmetric shaped and angulated aneurysms, or "stomach-shaped" aneurysms, are deemed to be at risk for type Ia endoleaks, especially in combination with a short infrarenal neck (Fig. 5). The increasing volume in the endobags forces the stent lying in the outer curve to move downwards and cause misalignment of the stent. Maintaining proper stent position is crucial at this point and optimally the endobags, located 4 mm below the stent, should be positioned immediately infrarenal. When stents tend to dislodge during prefill, inflation of the Nellix® balloons during filling will create more stability in the system. The addition of contrast to the prefill solution may also be helpful. During the procedure, angiographies are performed through the nose cones of the devices, but contrast density is lower compared to pigtail angiographies. It is advised to first remove one catheter and replace that with an angiography catheter and make a control angiogram in two directions. This enables the use of a secondary fill from another device, in case a minor endoleak is observed. A lateral view angiogram is important, because endoleaks may occur in the conjunction area of the two endobags, which could be missed on AP angiography.

Figure 5. Procedural angiography: 'stomach' shaped aneurysm (A). Two deployed Nellix® endografts with misalignment causing a type Ia endoleak (B).



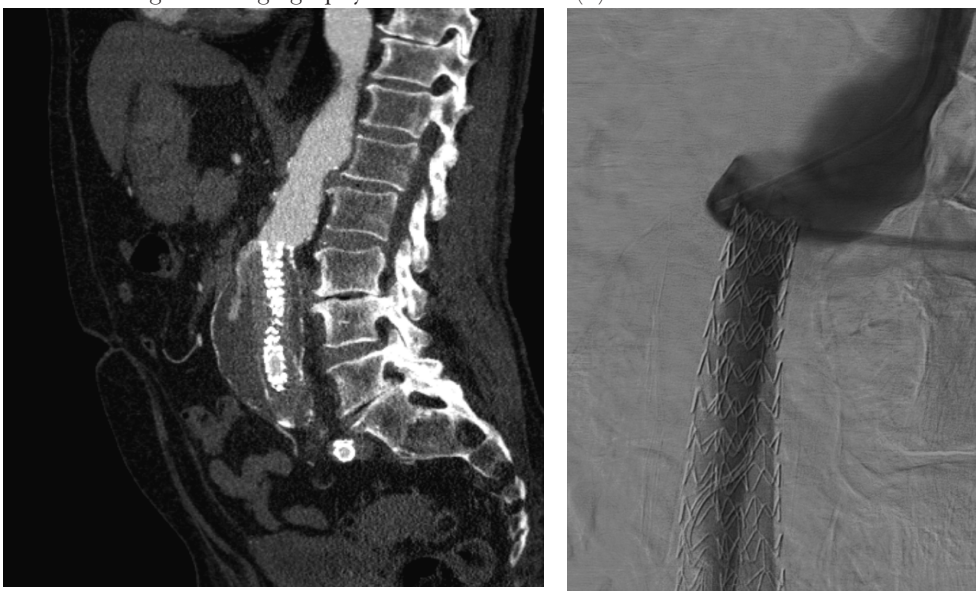
Detection of type Ia endoleaks after EVAS can be challenging because of the presence of the endobags. A type Ia endoleak can be recognized as contrast between the endobags and the aneurysm wall (Fig. 6a). This may be subtle and it can be difficult to differentiate from calcium or precipitated contrast in the endobag. Another possibility is contrast between the endobags (Fig. 6b), while an increasing amount of thrombus between the endobags during follow up can be considered as a warning sign. When in doubt, an ECG-gated CT scan can be of additional value in the detection of an endoleak, while this can also be visualized on duplex and MR angiogram[20].

Figure 6. Transversal views of a CTA show contrast between the endobag and the aortic wall (A) and on a different patient between the endobags (B).



Anecdotal information states that type Ia endoleaks are not benign, and tend to increase over time, potentially causing secondary aneurysm rupture. It is therefore advisable to treat type Ia endoleak early. Nevertheless, some type Ia endoleaks resolve spontaneously shortly after the procedure (Fig. 7).

Figure 7. Type Ia endoleak after EVAS on CTA in sagittal view (A). The endoleak spontaneously resolved on diagnostic angiography 3 weeks after CTA (B).



Treatment options include the embolization with coils in combination N-Butyl-Cyanoacrylate or Onyx treatment or N-Butyl-Cyanoacrylate /Onyx only in minor endoleaks (Fig. 8), or the extension of the endograft with another Nellix® stent in case of misplacement or distal migration (Fig. 9). A comprehensive description of N-Butyl-Cyanoacrylate application in EVAS patients has recently been published by Harvey et al[21]. Others have described their experience with trans-catheter embolization of type Ia endoleak after EVAS in seven patients[22]. The mean time from EVAS to embolization was 136 days. Embolization was performed with coils and Onyx in six and Onyx only in one case and technical success was achieved in all. One patient required a secondary procedure following Onyx reflux into the Nellix® endograft. All patients remained free of endoleaks with stable sac size after a mean follow-up of 8 months. In case of distal migration during long-term follow up proximal extension with another Nellix® stent, with or without chimney grafts, appears to be an attractive option, although this

technique is still in development. Flaring of the original stent with a 12 mm balloon as well as pre-deployment of the endobag before expanding the stents is advisable. The minimum required sealing length is yet to be determined,yet seems to be about 2-3 cm. Chimney grafts are therefore often required.

Figure 8. Dorsal type Ia endoleak after EVAS, treated with N-butyl-cyanoacrylate and proximal extension using two balloon expandable covered stents. (images courtesy of Andrew Holden, Auckland City Hospital, Auckland, New Zealand).

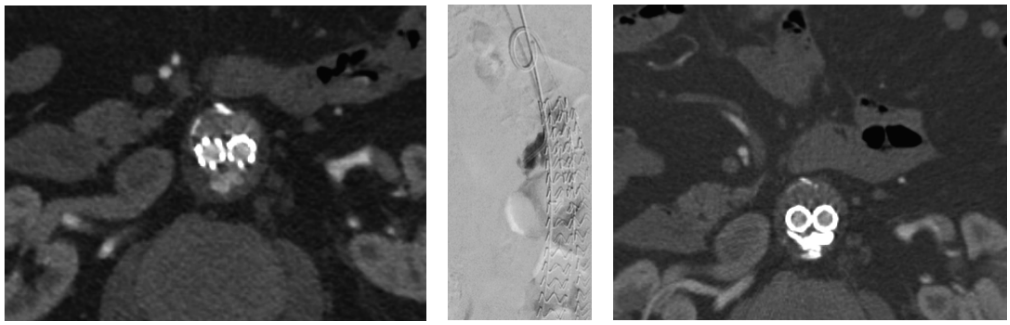
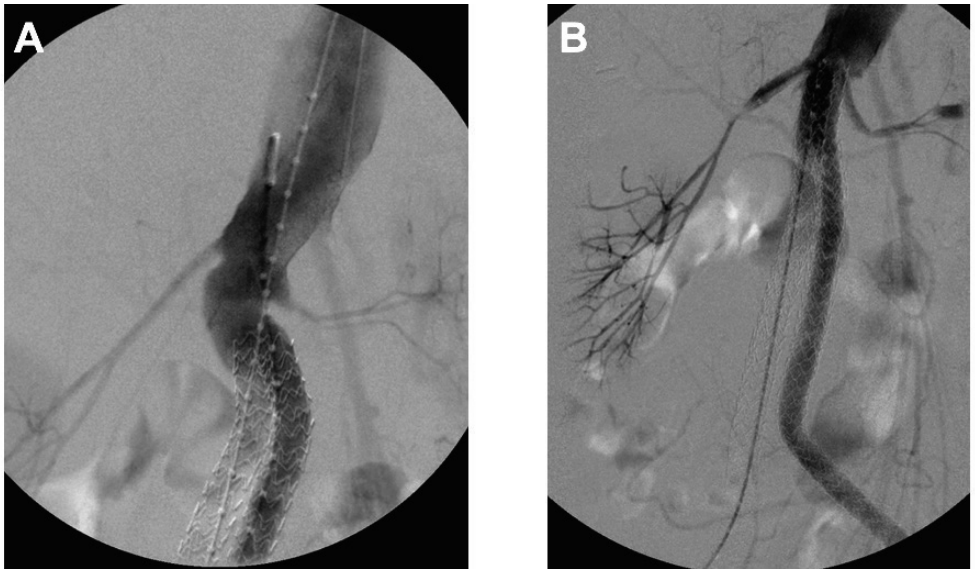


Figure 9. A distally migrated Nellix with a type Ia endoleak (A) treated by proximal extensions using two new Nellix stents and chimney grafts in the renal arteries (B).



SUMMARY

- Type Ia endoleaks are an important risk factor for secondary rupture after endovascular treatment of abdominal aortic aneurysms and treatment is usually indicated.
- Conventional CT-angiography is the primary diagnostic method but MRA or ECG-gated CT-angiography can be of additional value.
- Although treatment options for type Ia endoleak are available, the focus should be their prevention by proper patient selection and technique.
- Type Ia endoleak after endovascular aneurysm sealing (EVAS) seems to be related to a learning curve and early intervention is indicated.

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4.2

Circumference as an alternative for diameter measurement in endovascular aneurysm repair

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(Medical Hypotheses 2015;85:230-3)

ABSTRACT

Appropriate sizing of endografts for endovascular aneurysm repair has traditionally been performed by one standardized method. By measuring the average of the minor and major axes in the sealing zone, the endograft size is traditionally calculated. However, no adequate scientific evaluation has been performed to validate this method. The guidelines that were published are based on theories and experience, more than scientific evidence. In case the central lumen line artery cross-section is a circular disk, the vessel diameter is a reliable estimation. Yet the aortic neck cross-section may not always be geometrically a perfect circular disk. Application of the standardized method might therefore lead to inaccurate endograft sizing, potentially leading to endoleaks. We hypothesize that in these cases the circumference of the vessel is a mathematically correct reference to deduct the appropriate endograft diameter. The following formula was applied in this study: diameter of the corresponding circle (d) equals circumference (C) divided by π. This study provides a theoretical analysis of the mathematical implications of this method. Only in case of highly irregularly shaped cylinders, the circumference-based method was more accurate than the standardized method. Nonetheless, the circumferential method was a practical reference in case the aortic neck was irregularly shaped. Also, the circumference method was accurate in all cases in deducting the diameter of a matching circle. Therefore, the hypothesis that was raised in this study has a strong theoretical base. We predict that in case this hypothesis holds true in the clinical practice, application of the circumference method might lead to less endoleaks than the standardized method.

INTRODUCTION

Endovascular aneurysm repair (EVAR) implicates measurement of sealing zones proximal and distal to the aneurysm for optimal stent graft selection to ensure adequate sealing and fixation. Inappropriate sizing could in theory result in a higher incidence of endoleaks due to undersizing or oversizing with infolding of the endograft [1,2]. Traditionally, sizing of the artery to select the optimal endograft diameter was done by measuring the diameter of the artery in the axial slices of a computed tomography (CT) angiogram. However, when the artery is angulated with respect to the imaged slice, the axial CT shows an ellipsoid shaped section of the aorta. In that case the smallest wall-to-wall diameter in any direction of the artery is generally selected [3]. This technique, however, is correct only in cases where the artery is a perfect cylinder and the cross-section perpendicular to the central lumen line (CLL) of the artery is a perfect circular disk. Moreover, it is nowadays common-practice to measure blood vessel diameters on the CLL reconstruction images instead of on axial slices. When for reasons of angulation, atherosclerotic degeneration, or dissection, the artery is not a cylinder but instead more flattened in one direction, the axial central lumen line cross section will have the shape of an ellipse with a certain degree of eccentricity. In this event, it has been advised to estimate the vessel diameter by averaging the major and minor luminal axes [4]. It remains to be seen however, whether this is the best approach for determining vessel diameter and subsequently endovascular stent-graft size or whether an alternative approach may yield better results.

HYPOTHESIS

In order to achieve sealing, the outer surface of the endograft should be in apposition to the arterial luminal surface. The arterial circumference may therefore be the best determinant of graft size. For cylindrical arteries, the graft size may be calculated from the aortic neck diameter. This may be troublesome in necks with a non-cylindrical shape, potentially leading to endograft failure like endoleak type 1A. We hypothesize that the vessel circumference is a mathematically correct reference for the vessel diameter calculation and endograft diameter selection. This technique could be useful when the artery cross-section perpendicular to the CLL is not a disk. The circumference can be used to deduct the matching circle diameter. Subsequently, the matching circle diameter is the reference to select the stent-graft diameter.

TECHNIQUE

The area perpendicular to the CLL of a cylindrical artery is a circular disk. In that case the disk diameter is a good reference for endograft sizing. When the artery has a cylindrical shape, the circumference could also be used as a reference to deduct the matching diameter of the disk the section of the artery at that point is.

The circumference (C) of a circle with radius r is:

$$C = 2\pi r \quad (1)$$

In cases where the section perpendicular to the CLL of the artery is not a circular disk, there is not a single diameter of the artery at that point that is a good reference for sizing. The circumference of the artery section in this case is the best reference to deduct the corresponding circle diameter. Counter intuitively, the section area as opposed to the disk circumference can not be used as a reference to deduct the circle diameter. Figure 1 shows two geometric forms with equal circumferences and different areas. For apposition of the stent-graft to the arterial wall, it will have to follow the circumference rather than fill up the area. In both cases, the same stent-graft diameter would have to be chosen to gain apposition, as the circumference is the same whereas the area is smaller in the form following the concave dashed line as compared to the convex full line.

Figure 1. Illustration of two geometric forms simulating blood vessels and with different areas (shaded) but with a similar circumference.

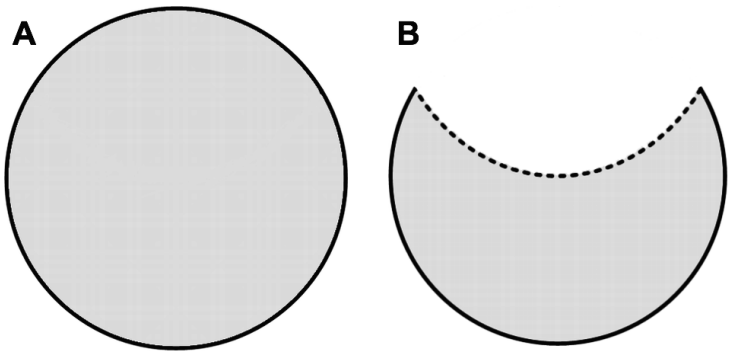


Figure 1A has the same circumference as figure 1B, but figure 1A has a much larger area than figure 1B.

With a perfect ellipsoid vessel shape, the ellipse can be described by major (2a) and minor axes (2b) lengths (Fig. 2). In the conventional method, the corresponding circle diameter (D) is approximated by the average of both axes lenghts:

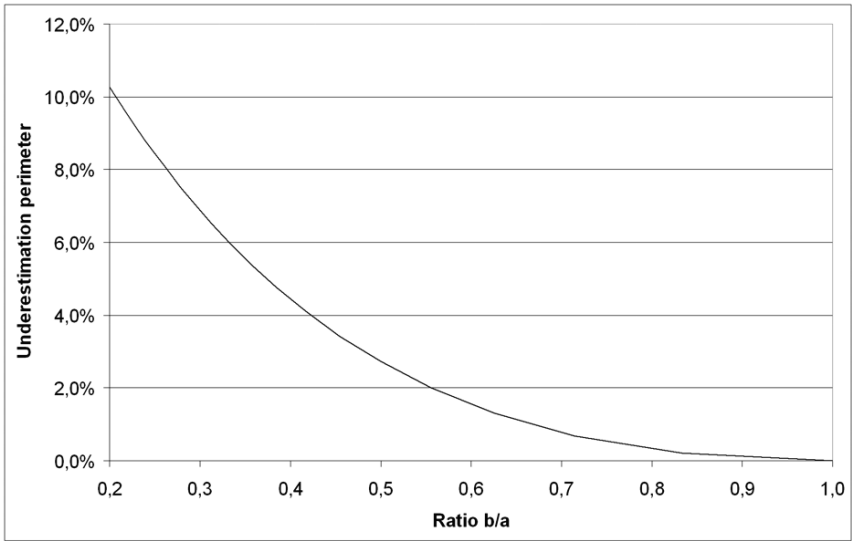
$$D = \frac{2a + 2b}{2} \tag{2}$$

To approximate the vessel diameter by using the circumference of the ellipse, one could use Ramanujan's approximation [5], and the corresponding diameter of the vessel is:

$$D = 3(a+b) - \sqrt{(a+3b)(3a+b)} \tag{3}$$

In Figure 2 the difference between the corresponding vessel diameters computed with the conventional method (average of axes) and with the proposed method (circumference) as a function of the ratio between major and minor axes of the ellipse is plotted. Although the proposed method gives a better approximation of the vessel circumference, the underestimation of the diameter by the conventional method only becomes > 5% when the ratio between the axes becomes < 0.37. (Table 1) This is true for an ellipsoid vessel with a severe eccentricity.

Figure 2. Function plot of the determination of the diameter of a circle with a circumference that corresponds with an ellipse with the same circumference.



Underestimation of the circumference of the ellipse, approximated by the average of the major axis (2a) and the minor axis (2b) (conventional method, P2), compared to Ramanujan's approximation5 (proposed method, P1), as a function of the ratio b/a.

Table 1.

Long axis ellipse (2a)	Short axis ellipse (2b)	Ratio short / long axis (b/a)	Eccen-tricity (e)	Ramanujan approximation of perimeter (P1)	Approximation perimeter 2π x average (a,b) (P2)	Under-estimation of perimeter ((P1-P2)/P1)
1.00	1.00	1.00	0.00	3.14	3.14	0.0%
1.20	1.00	0.83	0.55	3.46	3.46	0.2%
1.40	1.00	0.71	0.70	3.80	3.77	0.7%
1.60	1.00	0.63	0.78	4.14	4.08	1.3%
1.80	1.00	0.56	0.83	4.49	4.40	2.0%
2.00	1.00	0.50	0.87	4.84	4.71	2.7%
2.20	1.00	0.45	0.89	5.20	5.03	3.4%
2.40	1.00	0.42	0.91	5.57	5.34	4.1%
2.60	1.00	0.38	0.92	5.94	5.65	4.8%
2.80	1.00	0.36	0.93	6.31	5.97	5.4%
3.00	1.00	0.33	0.94	6.68	6.28	6.0%
3.20	1.00	0.31	0.95	7.06	6.60	6.5%
3.40	1.00	0.29	0.96	7.44	6.91	7.0%
3.60	1.00	0.28	0.96	7.81	7.23	7.5%
3.80	1.00	0.26	0.96	8.20	7.54	8.0%
4.00	1.00	0.25	0.97	8.58	7.85	8.4%
4.20	1.00	0.24	0.97	8.96	8.17	8.8%
4.40	1.00	0.23	0.97	9.34	8.48	9.2%
4.60	1.00	0.22	0.98	9.73	8.80	9.6%
4.80	1.00	0.21	0.98	10.12	9.11	9.9%
5.00	1.00	0.20	0.98	10.50	9.42	10.3%

This table provides the calculation of the diameter of a circle with a circumference corresponding with an ellipse with the same circumference. The conventional method (P2) was compared to the proposed method (Ramanujan's approximation[5] P1), as a function of the ratio b/a. In Figure 2 these calculations are plotted in a graph.

Let us now assume an irregularly shaped artery (Fig. 3) without an axis that is a good reference for the matching circle diameter. The circumference of the irregularly shaped form equals the matching circle with the same circumference. Practically, the artery circumference can be measured directly on the CLL axial reconstruction image.

Figure 3. Circumference of an irregularly-shaped vessel as plotted on an axial central lumen line CTA reconstruction image.

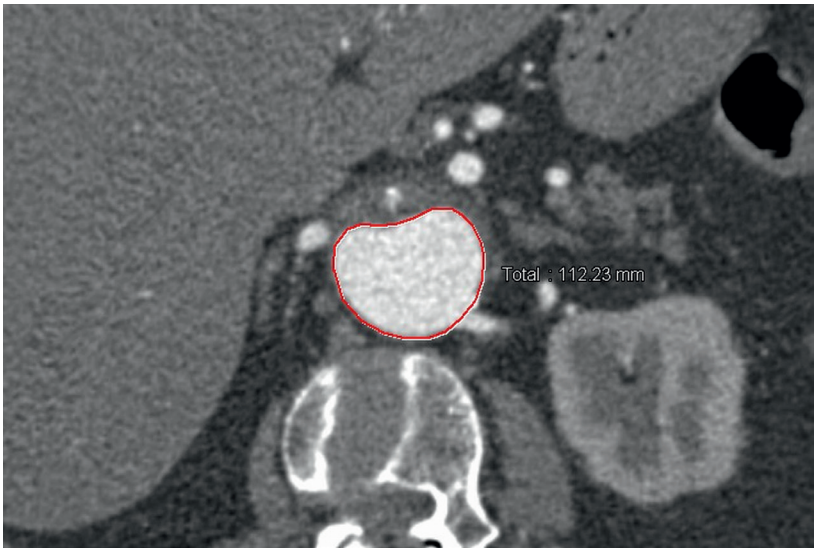
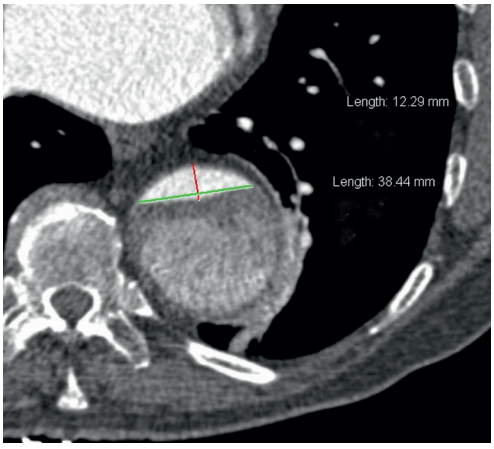
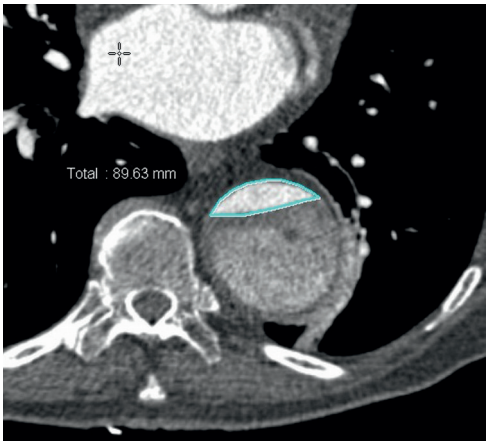


Figure 4. Example of determination of the circumference of the true lumen of a chronic dissection of the thoracic aorta using the average of minor and major axes (4A) and using the circumference of the true lumen (4B).





Average of axes equals (12.3 mm + 38.4 mm)/2 = 25.3 mm.
Circumference is 89.6 mm; the corresponding circle diameter is 28.5 mm, which is 12.6% more than with the average of axes method.

With the circumference data, the corresponding circle diameter can be calculated as is illustrated in Figure 4:

$$d = \frac{C}{\pi} \qquad (4)$$

EVALUATION OF THE HYPOTHESIS

This report illustrates the validity of the hypothesis of the artery circumference as a reference for sizing and planning in EVAR. In the literature dating back from 1991 when the first EVAR cases were reported [6], no guidelines have been described for sizing in EVAR planning. The biggest challenge in selecting appropriately sized endografts is when the artery cross-section perpendicular to the CLL is not a circular disc. In these cases, this report suggests that the artery circumference (C) is the best reference for deducting the matching circle diameter (d): $d = \frac{C}{\pi}$.
Based on this diameter, the endograft diameter can be selected, taking into account the degree of oversizing as indicated by the device manufacturer in the instructions for use [7]. The theoretical analysis in this report has interesting implications. First, it shows that with an ellipsoid shaped artery cross-section, the average of major and minor axes is a good reference for endograft sizing, except when the eccentricity of the ellipse is significant. Second, circumference is a practical reference for endograft diameter selection in cases where the arterial cross section is irregular. Finally, the artery circumference can in all cases be used as an accurate test and reference to deduct the diameter of the matching circle. Application of this theory in real world sizing may include vessel diameter measurement in a chronic dissection with a highly flattened true lumen; inner vessel diameter measurement for a fenestrated stent-graft design and where the artery lumen (without thrombus) is irregularly shaped (Fig. 3); determining the size of limbs that can be accommodated by a narrow aortic bifurcation. Specific implications will be subject of future research.

Limitations in the technique's applicability may be in the restricted endograft compliance with regards to the artery wall, meaning that it is not clear whether the endograft will always adapt fully to the artery circumference. In cases as depicted in

Figure 4, the behaviour of the endograft in the true lumen of a chronic dissection is uncertain, especially with regards to the compliance of the endograft in the sharp corners, and to the effect on the intimal flap.

In theory, the corresponding diameter of the lumen is best computed based on the circumference. On the other hand, in most cases either the diameter or the average of major and minor axes is a good reference for sizing the endograft diameter. This hypothesis will have to be studied in a clinical setting to validate its practical relevance. In the field of aortic valve replacement, the implications of the circumference measurement versus the diameter measurement have also been studied. The aortic annulus is also more often elliptical rather than perfectly circular. Two studies show that circumference measurements and a circumference-based area measurement might improve aortic annulus sizing and perhaps minimize aortic regurgitation [8,9]. This implies that the theoretical nature of our mathematical hypothesis has practical consequences across multiple surgical fields. If our hypothesis is true, we predict that the circumference technique might be more effective in measuring aortic necks for endograft sizing compared to the traditional method. A prospective study with randomized use of the applied method, although impossible to perform double blind, is the best approach to validating this hypothesis in practice.

CONCLUSIONS

Selection of endograft diameter for EVAR is traditionally based on measurements of the artery diameter. In some cases, the circumference of the artery is an effective alternative to calculate the corresponding circle diameter. This is especially the case when the cross-section of the artery is not a circular disk. This technique may help solving problems in selecting the appropriate endograft diameter in aneurysms with an irregular sealing zone. Additional research regarding clinical value and implications is needed.

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4.3

Endograft sizing for endovascular aortic repair and incidence of endoleak type 1A

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(PLoS One 2016;11:e0158042)

ABSTRACT

Objective: In endovascular aortic aneurysm repair (EVAR), proximal type 1A endoleaks can occur as a result of hostile neck anatomy or over- or undersizing of the endograft. As the current standard is based on the diameter or average of the short and long axes in a central lumen reconstruction image, it can falter in irregularly shaped aortic necks. An alternative method is circumference-based, therefore minimizing the measurement error. In this study we aimed to assess the degree of discrepancy between both methods and the association of this discrepancy with the occurrence of endoleak type 1A.

Methods: All patients with early (<30 days post-operative) endoleak type 1A after elective EVAR at our center between 2004 and 2016 were identified for a retrospective case-control study. Control patients were matched based on hostile neck anatomy, such as calcification, thrombus, reverse taper, and β-angulation. The aortic neck diameter was measured using the traditional, diameter-based method as well as an alternative method, based on the circumference of the aortic neck.

Results: In 482 EVAR patients, 18 early endoleak type 1A cases were found (3.9%). After exclusion, 12 cases remained and 48 matching controls were found. No significant differences were found between the two measuring methods at any level below the renal arteries. The inter-observer variability was significant for the D(mean) (0.4 ± 1.69 mm, P = .02) and was larger than the D(circ) method (-0.1 ± 1.03 mm, P = .35). In only four out of 12 cases the endograft size was 10-20% larger than the D(mean) and D(circ) measurements. The differences between the diameter of the D(mean) and D(circ) and the chosen endograft were smaller for the case group (-8 ± 25.6% and -7 ± 24%) than for the control group.(-12.4 ± 12.4% and -11 ± 10.7%).

Conclusion: The difference between the D(mean) and D(circ) methods for aortic neck measurement was not large enough to play a significant role in the incidence of endoleak type 1A. Inadequate oversizing and considerable β-angulation of the aortic neck may have been the cause of endoleak type 1A in this population. Robust and well-investigated sizing methods are paramount for accurate endograft sizing and prevention of endoleak type 1A. Therefore the lack of studies in this field and a sizeable inter-observer variability do not justify the widespread reliance on the traditional diameter-based methods for endograft sizing.

INTRODUCTION

The introduction of endovascular techniques for the treatment of abdominal aortic aneurysms (AAA) has lead to a decrease in perioperative mortality. With regard to long-term postoperative mortality, endovascular aortic repair (EVAR) is on par with open repair [1,2]. However, in terms of complications patients treated with EVAR have a three- to fourfold higher rate of graft-related morbidity than patients treated by open repair [3]. A large part of EVAR-related complications is due to endoleaks. In the case of endoleak type 1A, the endograft does not completely seal the proximal aneurysm neck and arterial flow is present between the wall of the aortic neck and the graft material. This flow may lead to further growth and eventually rupture of the aneurysm. The incidence of endoleak type 1 can be partially attributed to the surgical skill of the surgeon, as well as to the skill for preoperative sizing of the endograft [4]. Hostile neck characteristics have also been associated with the occurrence of endoleak type 1A. These characteristics include a short proximal aneurysm neck length, reverse tapering of the neck, mural calcification or thrombus, and severe neck angulation [5]. Endografts are currently sized by determining the diameter of the aortic neck. This is measured by averaging the diameter of the longest and shortest axis of the infrarenal aortic neck. Since the introduction of EVAR, this has been the only method to size endografts. As the diameter-based method has always been considered to be the best and no comparative studies have been performed so far, it is conceivable that there are other, more accurate methods available. In cases where the central lumen line of the aortic neck section is not a perfect circle, the abovementioned method will yield some mathematical incorrectness. Recently, a different and mathematically more correct measurement of the diameter of the aortic neck, based on the circumference of the neck, has been proposed. Theoretically, both methods produce similar results as long as the section of the aortic neck has a perfect circular shape. However, as aortic neck cannot be perfectly circular, there will always remain a discrepancy between the results of the two methods [6]. Still, the impact of this discrepancy for potential clinical use of both methods is unclear. Also, most endograft manufacturers recommend that the diameter of the endograft should be 10-20% larger than the diameter of the aortic neck, also known as "oversizing". In a systematic review, Van Prehn et al. evaluated risks and benefits of oversizing [7]. The authors concluded that the evidence

for a correlation between oversizing and incidence of endoleak type 1A is limited, but oversizing between 10-20% is recommended and "relatively safe". Theoretically, adequate oversizing should negate any clinical consequences of the discrepancy between the current method and its alternative, but this has never been studied. The aim of our study was to assess the degree of discrepancy between both methods and the association of this discrepancy with the occurrence of endoleak type 1A. To this end, the traditional diameter-based method and the alternative circumference-based method were compared in a retrospective, case-control set-up.

METHODS

Study design

The aim of this study was to assess the discrepancies between both methods and the association of this discrepancy with the occurrence of endoleak type 1A in a retrospective case-control set-up. Two methods for sizing the aortic neck diameter were retrospectively applied to an endoleak type 1A (case) group and a matched control group. For both case and control subjects, demographic and clinical data were gathered. These included sex, age, smoking habits, history of cardiovascular disease and/or diabetes mellitus type 1 or 2, peri- and postoperative complications, peri- and postoperative treatment of endoleak type 1A, death following intervention, and aneurysm morphology. For additional information on the endografts that were chosen as part of routine clinical care, the manufacturer brand and endograft size were collected. For this project, the Medisch Ethische Toetsingscommissie (Medical Ethics Committee) of the University Medical Center Groningen approved this study (number 201500390) and decided that no informed consent was required.

Patients

All subjects were collected from a database of AAA patients who underwent elective EVAR treatment between January 2004 and January 2016. Case subjects with an endoleak type 1A that were identified by a vascular surgeon during or early after (<30 days) EVAR treatment, were included in the study. Late endoleak type 1A cases were excluded, as these cases are commonly a result of ongoing aneurysmal disease. The inclusion criteria for case subject eligibility were as follows: 1. Identification of an

endoleak type 1A diagnosed intraoperatively or on the first computed tomography angiogram (CTA), routinely performed four weeks postoperatively; 2. The availability of CTA data. Case and control subjects that had undergone EVAR treatment for impending or acute aneurysm rupture were excluded from this study. Patients who received custom made endografts because of severe anatomic restrictions were also excluded.

Control subjects were EVAR-treated patients with no post-operative complications, and were matched to the cases based on hostile neck anatomy characteristics.4 Matching was performed to correct for the previously described association of these confounding factors with the occurrence of endoleak type 1A. Hostile neck anatomy was defined as having at least one of the following anatomical characteristics of the aortic neck: length <10 mm, tapering >2 mm per 10 mm of length, diameter >28 mm, >50% neck circumference lined with thrombus, >50% neck circumference lined with calcification, and the β-angle between neck and aneurysm of >60 degrees [8-13]. Each case subject was paired with control subjects based on their configuration of hostile neck anatomy characteristics. Because of the low incidence of endoleak type 1A, a ratio of four controls for each case was chosen to maximize the statistical power [14].

Computational aortic neck measurements

The aortic neck diameter was measured with two methods. Mathematical equations and definitions are explained to provide full understanding of the study design. Sizing of endografts is generally performed by measuring the diameter (D) of the aortic neck (Fig 1). In cases where the axial plane of the neck is not a perfect circle, the average of long and short axes are used to calculate the diameter of the corresponding circle:

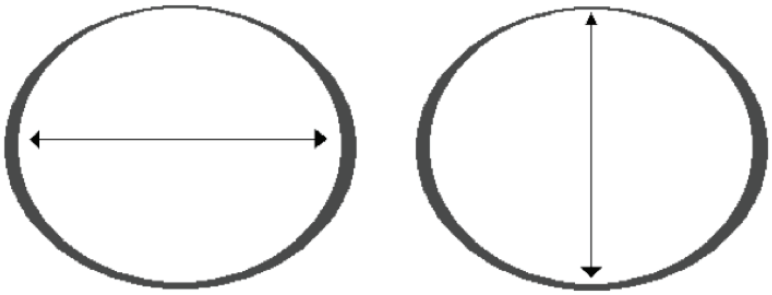
$$D(mean) = (long\ axis + short\ axis) \div 2 \quad (1)$$

In theory, the circumference (C) of the aortic neck can also be used to calculate the diameter of the corresponding circle:

$$D(circ) = \frac{C}{\pi} \quad (2)$$

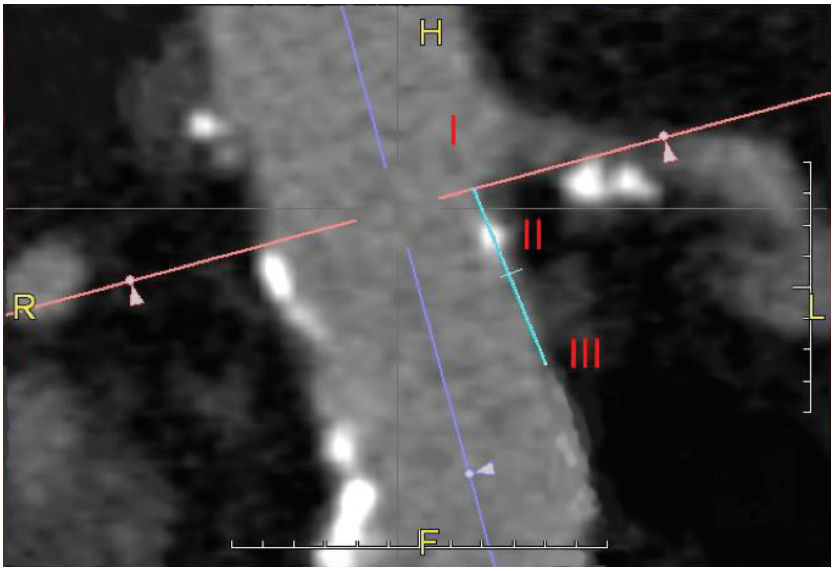
Both the D(mean) and D(circ) were determined at three levels of the aortic neck: at the level just below the distal border of the most distal renal artery (0 mm, height I), at 7.5 mm (height II), and 15 mm (height III) below this level. (Fig 2) At each of these locations, relevant sections were selected based on the center lumen line. The D(circ) method was performed by manually tracing the aortic wall using the software-specific digital calipers. The degree of thrombus, calcification, tapering, and angulation were measured as described in earlier reports [8,10-12]. Two observers, including the main investigator (first author) and an experienced (endo)vascular surgeon (last author) were instructed on how to perform both methods and were blinded to the groups. Blinding was achieved through randomizing the order of the subjects in the database before measuring. The results of the D(mean) and D(circ) methods obtained by the main investigator and the expert were compared to evaluate the inter-rater reliability of both methods. Differences between observers, methods, and between case and control groups were considered clinically relevant in case they exceeded 10%, based on the fact that this is considered the lower threshold for adequate oversizing [7]. To enable case matching with controls, all subject CTA data were analyzed using AquariusNet Viewer Client V4.4.4.23 (TeraRecon, Foster City, CA, USA) on a 24-inch NEC MultiSync EA241WM monitor. This was performed orthogonally to a center line using multi planar reformat views (Fig 3). The neck length was measured computationally as the distance between the distal border of the lowest renal artery and the proximal start of the AAA. An angulation measurement method based on the method by van Keulen et al. was performed using a manually adjusted estimation of the central lumen line [12]. The angle between the anticipated landing zone of the endoprosthesis and the aneurysm sack (β angle), was measured. Calcification was identified as high attenuating signals (>140 Hounsfield units) within, or closely aligned with, the vessel wall. It was then graded as either more or less than 50% circumferential calcification at the anticipated landing zone [4]. Low attenuating signals lining the lumen of the vessel wall were identified as thrombus. Thrombus was graded as either more or less than 50% circumferential thrombus with a thickness of >2 mm [12]. Reverse tapering was defined as an increase in neck diameter of >2 mm over a length of 10 mm [10].

Figure 1. Visual representation of the aortic neck diameter assessment method according to the current standard.



The average of long (left) and short (right) axis provide the diameter of the corresponding circle.

Figure 2. Computed tomography image of the abdominal aorta.



In Roman numerals the infra renal distances are portrayed. I: 0 mm, II: 7.5 mm, and III: 15 mm. To provide a standardized method for measuring the distances as mentioned above, first the midline of the aortic neck is chosen. The perpendicular line is then placed at the point where the lowest renal artery branches from the aorta. In the caudal direction from this point (I) and parallel to the midline, a distance of 7.5 and of 15 mm is measured to identify point II and III, respectively.

Statistical analysis

The sample size of this study was chosen based on the incidence of early endoleak type 1A in our EVAR-treated patient population, following the above-mentioned inclusion and exclusion criteria. A post-hoc power analysis was performed using G*Power 3.1.9.2 for Mac OS X (University of Düsseldorf, Düsseldorf, Germany) to assess whether the group sizes were adequate to reliably calculate the degree of significance [15]. The primary endpoint for this study was the difference in diameter (mm) between D(mean) and D(circ). Categorical data were tested in cross-tabs using the chi-square test and Mantel-Haenszel matched-pairs analysis. Continuous data were analyzed using paired t-tests if normally distributed. In case of skewed distribution of data, the Wilcoxon signed rank sum test was used. Inter-observer variability and the variability between the D(mean) and D(circ) method were calculated through paired-samples t-tests and visualized in Bland-Altman plots. Results were reported as a percentage for categorical data, mean ± standard deviation (SD) for continuous data, and median and interquartile range in case the data had a skewed distribution. Significance was set at $P < .05$. Statistical analyses were performed using SPSS 20 (Statistical Package for the Social Sciences, IBM, Armonk, NY, USA).

Post-hoc power analysis

To calculate the effect size (d), means and standard deviations of the D(mean) measurements were used, providing a d of .47. Given the sample sizes of both the case and control group and an α of .05, the post-hoc power was calculated to be at .3. As the minimally acceptable power is set at .8, the statistical significance of potential differences is not representative of the general population. All the diameters from height I to III were compared for the inter-observer variability and the paired-samples t-test for the variability between the D(circ) and D(mean) method. These could be reliably tested for significance, as the number of unique diameter measurements was tripled.

RESULTS

Demographics and clinical information

Comparison of endoleak type 1A patients to controls is only reliable if the differences in demographic and clinical variables are small. Patients were stratified based on

incidence of endoleak type 1A, and clinical data. Twenty-three out of 482 patients planned for elective EVAR underwent acute treatment for a ruptured or symptomatic aneurysm and were excluded from the study. Of the 459 remaining elective patients, 18 (3.9%) were diagnosed with an early endoleak type 1A. In four patients CTA data were missing and two patients had received custom made endografts, leaving 12 endoleak type 1A patients for CTA analysis. After matching for hostile neck anatomy, 48 patients without complications were found as control cases (Fig 3). Minor differences between both groups were found in age, sex, and cardiovascular history. Most notable was the fact that the incidence of diabetes mellitus type 1 or 2 was 10% higher in the control group than in the case group. The maximum diameters of the AAA did not differ significantly between the two groups (Table 1). Inter-observer variability was significant for the D(mean) (0.4 ± 1.69 mm, P = .02) and larger than for the D(circ) method (-0.1 ± 1.03 mm, P = .35) (Figs 4 and 5). The greatest part of the observations for both methods is within the 95% limits of agreement. However, the 95% limit spans 3.37 mm for the D(mean) method or a 14% difference to the average D(mean) measured in this population. For the D(circ) method the 95% limit spans 2.05 mm, which is an 8.1% difference to the average D(circ) measured in this population.

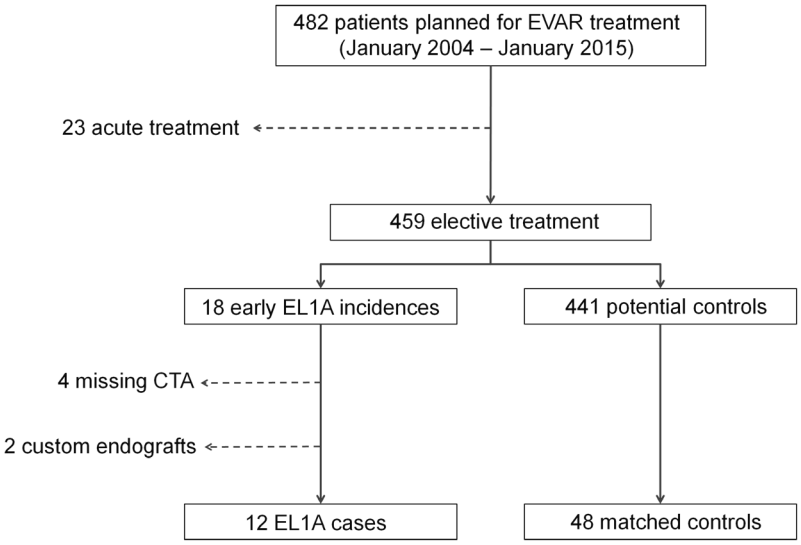
Table 1. Demographic characteristics of case and control groups

Variable	Endoleak type 1A (n = 12)	Controls (n = 48)
Age (y)	75.8 ± 11.9	71.8 ± 7.7
Male sex (%)	75	89.6
History of cardiovascular disease (%)	75	72.9
History of diabetes mellitus type 1 or 2 (%)	8.3	18.8
AAA diameter (mm)	64.4 ± 14.8	62.7 ± 13.2
Graft (Brand/Type)		
Gore/Excluder (%)	25	41.7
Cook/Zenith (%)	50	50
Vascutek/Anaconda (%)	25	8.3
Compliance to the Instructions For Use (%)	83.3	79.2

AAA: abdominal aortic aneurysm

y: years

Figure 3. Flow chart of the population selection in this study.



Of the 482 patients with AAA who were selected for EVAR treatment, 23 received acute intervention and were excluded. EL1A was found in 18 patients, two of which received custom made endografts and in four cases the CTA images were missing. These were therefore excluded. Of the 441 remaining EVAR, 48 controls were selected based on matching for hostile neck anatomy.

AAA: abdominal aortic aneurysm.

EVAR: endovascular aneurysm repair.

EL1A: endoleak type 1A.

CTA: computed tomography angiography.

Fig 4. Bland-Altman plot of the differences between observer A and B for the D(mean) method.

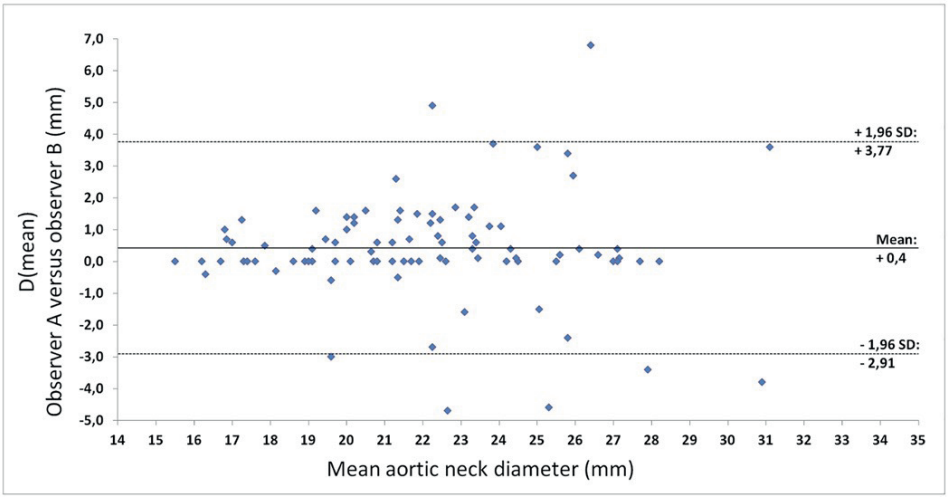
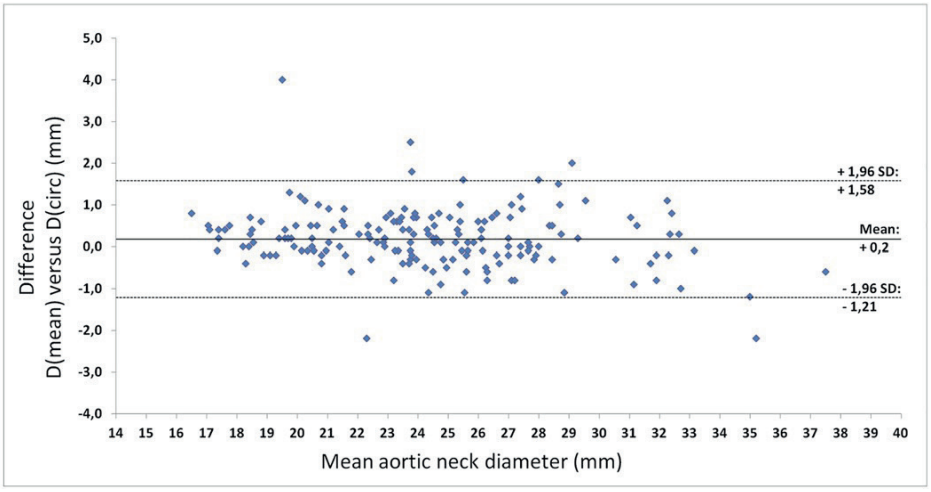


Fig 5. Bland-Altman plot of the differences between D(mean) and D(circ) measurements of both observers.



Characteristics of endoleak type 1A patients

Clinical, anatomical, and graft-related characteristics at individual level can be valuable in assessing the risk to develop endoleak type 1A. The hostile neck characteristics and treatment of all endoleak type 1A patients are shown in Table II. Nine patients (75%) had ≥40° β-angulation of the aortic neck and for three patients (25%) this was ≥60°. Three others had a >50% calcified aortic neck circumference. No other hostile neck anatomy characteristics were found. Although the annual endoleak type 1A incidence in

this population is spread out evenly between 2004 and 2012, three cases were found in 2013 alone and none from 2014 to 2016. In two cases, the endograft required additional ballooning for the endoleak to diminish, but in none of the cases the endoleak had disappeared perioperatively. With and without ballooning, watchful waiting proved adequate on the first CTA two months after the intervention in 10 out of 12 cases. For two patients, an additional intervention was needed. In one case the endoleak type 1A was treated by open surgery and aortic banding and in the other case the endograft was extended proximally with a fenestrated cuff. In both cases the endoleak had disappeared after the second intervention.Table III shows that the D(mean) and D(circ) measurements differed by -3.1 to 5.3% from each other. In comparison to the endograft diameter, the D(mean) measurements were between 13.7% larger to 16.8% smaller. D(circ) measurements were between 12.4% larger to 13.8% smaller than the oversized endografts. In only four out of 12 cases the endograft size was 10-20% larger than the D(mean) and D(circ) measurements.

Table 2. Characteristics and treatment of endoleak type 1A in the case group.

EL1A case	Year	Brand	Neck angle	≥50% thrombus	≥50% calcified	≤10 mm length	Reverse taper	>28 mm neck diameter	EL1A Treatment
1	2004	Cook	50°	No	Yes	No	No	No	WW
2	2006	Cook	80°	No	No	No	No	No	WW
3	2007	Cook	50°	No	Yes	No	No	No	Aortic banding
4	2008	Cook	45°	No	No	No	No	No	Ballooning + WW
5	2009	Cook	100°	No	No	No	No	No	Ballooning + WW
6	2009	Cook	30°	No	No	No	No	No	WW
7	2010	Vascutek	90°	No	No	No	No	No	WW
8	2011	Vascutek	55°	No	No	No	No	No	WW
9	2012	Gore	40°	No	Yes	No	No	No	WW
10	2013	Gore	35°	No	No	No	No	No	Fen. cuff ext.
11	2013	Vascutek	55°	No	No	No	No	No	WW
12	2013	Gore	20°	No	No	No	No	No	WW

EL1A: endoleak type 1A
WW: watchful waiting
Ballooning: extra ballooning of the endograft in the aortic neck
Fen. cuff ext.: extension of the endograft using a fenestrated cuff

Table 3. Case group neck measurements, endograft size, and comparisons.

EL1A case	D(mean) average (mm)	D(circ) average (mm)	Diff. D(mean)-D(circ) (%)	Endograft diameter (mm)	Diff. Graft-D(mean) (%)	Diff. Graft-D(circ) (%)
1	26.5	27.9	5.3	26	1.9	6.8
2	29.0	28.9	-0.3	26	10.3	10.0
3	25.5	25.4	-0.4	24	5.9	5.5
4	27.8	27.4	-1.4	24	13.7	12.4
5	25.7	25.6	-0.4	24	6.6	6.3
6	29.7	30.5	2.7	30	-1.0	1.6
7	24.0	24.6	2.5	28	-16.7	-13.8
8	32.7	31.7	-3.1	34	-4.0	-7.3
9	19.7	20.4	3.6	23	-16.8	-12.8
10	25.2	25.7	2	28	10	8.2
11	20.9	20.9	0	30	30	30
12	21.6	22.1	2.3	23	6.1	3.9

Diff: difference
EL1A: endoleak type 1A

Differences between abdominal aortic neck measurements using D(mean) versus D(circ)

The D(mean) and the D(circ) measurements were compared first. The diameters measured by D(mean) (25.0 ± 4.1 mm) were on average 1.2% smaller than those of the D(circ) method (25.3 ± 3.9 mm). The aortic neck diameters at the different levels (0 mm, 7.5 mm, and 15 mm below the lowest renal artery) were slightly larger in the case group, although not significantly (Table 4). The differences between the two methods were tabulated for both the case and control group (Table 5). The difference between the two methods was small and was not consistent among the three distances below the renal arteries. The differences between the diameter of both the D(mean) and D(circ) and the chosen endograft were smaller for the case group (-8 ± 25.6% and -7 ± 24%) than for the control group.(-12.4 ± 12.4% and -11 ± 10.7%). Although on average the 10-20% oversizing rule was upheld for the control group, the average percentage of oversizing was inadequate for the case groups.

Table 4. Comparison of D(mean) and D(circ) measurements and endograft size.

Variable	Endoleak type 1A (n= 12)	Controls (n= 48)
D(mean) (mm)		
0 mm infrarenal diameter	25 ± 5	23.5 ± 3.8
7.5 mm infrarenal diameter	25.5 ± 4.1	23.9 ± 4.1
15 mm infrarenal diameter	26.6 ± 4.3	24.4 ± 4.4
Mean diameter	25.7 ± 3.8	23.9 ± 3.8
D(circ) (mm)		
0 mm infrarenal diameter	25.5 ± 4.6	23.7 ± 3.8
7.5 mm infrarenal diameter	25.7 ± 4	24 ± 4
15 mm infrarenal diameter	26.6 ± 3.9	24.8 ± 4.0
Mean diameter	26.9 ± 3.4	24.8 ± 4.1
Endograft diameter (mm)	27.1 ± 3	26.6 ± 3.1

Table 5. Differences between methods and endograft size in case versus control groups.

Variable	Endoleak type 1A (n = 12)	Controls (n = 48)
Difference of D(mean) and D(circ) (%)		
0 mm infrarenal diameter	-2.3 ± 4.5	-0.9 ± 2.3
7.5 mm infrarenal diameter	-1.0 ± 2	-0.6 ± 2
15 mm infrarenal diameter	-.2 ± 3.5	-2.4 ± 8.5
Difference of endograft size and D(mean) (%)	-8 ± 25.6	-12.4 ± 12.4
Difference of endograft size and D(circ) (%)	-7 ± 24	-11 ± 10.7

DISCUSSION

This study aimed to investigate the degree of discrepancy between the traditional endograft sizing method versus an alternative method and to potentially associate this discrepancy with endoleak type 1A incidences. Although preoperative sizing of the aortic neck anatomy has become a routine task in the field of vascular surgery, little research has been done on how this should be performed optimally. Most companies that manufacture endografts for EVAR state that adequate sizing is the responsibility of the physician [16]. Some companies provide more detailed guidelines on how to perform diameter measurements, without providing evidence supporting the technique that should be used [17]. As a consequence, the skills of the clinician performing the measurements might influence the incidence of endoleak type 1A. To our knowledge, no studies have been performed regarding the method of preoperative sizing for EVAR patients. Many studies have been performed in the field of oversizing, though none have gone back to the measuring methodology [7].

Our data have shown that D(mean) and D(circ) yielded similar results. Not only between the case and control group, but also when comparing both methods. Consequently, using either of these methods for diameter measurements is not likely to result in clinically relevant differences. However, in the case group the endografts were inadequately oversized in 10 out of 12 patients. This corroborates earlier studies on oversizing decisions for endografts. As published by Van Prehn et al, oversizing of 10-20% should lead to a minimum of graft migration, folding, or endoleak [7]. Oversizing increases the radial force of the endograft, thus tightening the seal between graft and aortic wall, and alleviates the effects of the elliptic shape on erroneous diameter estimation. The D(mean) of an ellipse always underestimates the true diameter of the corresponding circle with the same circumference [6]. This study shows that this underestimation was practically not relevant, so adequate oversizing should be able to correct for this. On the other hand, aggressive oversizing can also be associated with complications, such as endoleak due to fabric pleats. This could have been the case for one endoleak type 1A patient in this population, whose endograft was oversized by 30%. Thus, it remains unclear what "adequate" oversizing is. Since it is up to the surgeon to choose what exact percentage in the 10-20% oversizing range should be taken for the endograft, there is

sizeable potential for error. Remarkably, most of the endoleak type 1A cases received endografts with smaller diameters than both the D(mean) and D(circ) provided in this study.

Previously described incidences of endoleak type 1A ranged from 7.5 to 10.5%, although incidences as low as 0% and as high as 30% have been reported [5,18,19]. This shows that despite the rarity of endoleak type 1A, there is great variation in incidence between studies. The fact that the incidence of endoleak type 1A in our centre was lower than that reported in previous studies could be explained in several ways. During the entire study period, fenestrated grafts have been used to treat short neck AAA. The lower incidence of EL1A could therefore have been the result of a careful consideration of choosing fenestrated grafts or open repair instead of standard infrarenal EVAR in case of suboptimal aortic anatomy.

There were several notable results and trends that might have shaped this endoleak type 1A population. Most importantly, all case patients' aortic necks had medium to severe β-angulation, some of which were over 90 degrees, but most over 40 degrees. Instructions for use (IFU) for most endografts generally consider a β-angulation of over 60 degrees as less favourable and therefore a contraindication [4,10,20]. This degree of angulation is part of the hostile neck anatomy characteristics and has been proven to increase the risk of endoleak type 1A. Therefore, severe angulation could partly explain why a proportion of the study population developed endoleak type 1A. However, the control group was matched on all hostile neck anatomy characteristics, thus angulation could only have made a minor contribution to endoleak type 1A risk in this population. Final noteworthy aspects to this population are the treatment strategy and the resulting success. Watchful waiting for most cases and additional ballooning of the neck in two cases were sufficient to treat the endoleak. These outcomes seem particularly benign when contrasted to previous studies. Previous risk assessments of endoleak type 1A described aneurysm growth as a result of persisting endoleak type 1A, therefore increasing the risk of post-EVAR aneurysm rupture [3,21]. This is the first study to compare the current standard for aortic neck measurement with an alternative method. Two studies investigated several approaches to the pre-operative sizing of an endograft for transcatheter aortic valve replacement. Although neither study proposed

that the D(circ) method is optimal, both concluded that further studying of different sizing methods is warranted because of the variety in shapes of endograft placement sites [22,23]. Since the D(circ) method is mathematically more accurate than the traditional D(mean) method, it would make sense to further study its role in clinical practice. For prospective studies, our results should help to assess an adequate population size and period of time to maintain a power of at least 0.80. To reach the required number of EL1A cases, assuming a similar incidence, EVAR treated patients of at least three high volume vascular surgery departments should be prospectively followed for a period of 11 years. The influence of observer bias in endograft sizing should not be underestimated. The D(mean) method was found to have a sizeable discrepancy between observers, potentially skewing the measurements by 14%. As this is well beyond the lower limit of safe oversizing, there is a considerable risk that inter-observer variability alone could lead to undersizing or too aggressive oversizing in some patients. This discrepancy was even seen despite the fact that measurements were performed in a highly controlled standardized setting, with consistent use of the central lumen line. It could therefore be expected that this inter-observer variability will be more pronounced between different surgical teams and under routine clinical circumstances. It might be possible to diminish this variability if the aortic neck diameter were to be automatically calculated by the applied measurement software. Kaladji et al. have studied a three-dimensional sizing software (Endosize) based on CTA images, and concluded that it may be as reliable as the current standard [24]. Regrettably, this is only one tool that has not been clinically validated yet, so decreasing inter-observer variability through widespread use of an automated endograft sizing tool may not happen for quite some time.

Several limitations to this study should be addressed. The retrospective approach was chosen after evaluation of its potential and limitations. Retrospective studies are prone to be affected by loss of information and selection bias. In this case, detailed information on the original endograft sizing measurements and technical reasoning of the respective surgeons in the preoperative phase were missing. However, retrospective studies are efficient and known to be more useful for phenomena with a very low incidence, such as endoleak type 1A. Selection bias was concomitantly minimized by matching for demographic, clinical, and known risk factors for endoleak type 1A. Observer bias too was minimized by blinding the observers to the patient groups. Another limitation is

the fact that of the 18 patients with an endoleak, 22% were excluded because CTA data were missing. The fact that technical issues would diminish the case-population by this extent was unforeseen but irreparable. As our population of endoleak type 1A was too small considering the power analysis, statistical significance should be scrutinized and cannot be interpreted as a good representation of the relevant population. Nonetheless, to increase the clinical relevance of the descriptive data in this study, the power of the statistical analyses was increased to the fullest possible extent within the limited number of cases by matching with a 1:4 ratio [14].

CONCLUSION

In summary, the difference between the D(mean) and D(circ) methods for aortic neck measurement was not large enough to have played a significant role in the incidence of endoleak type 1A. The data provided by this study potentiate further validation of the current standards in a prospective cohort. Inadequate oversizing, in combination with considerable β-angulation of the aortic neck may have been the cause of endoleak type 1A in this population. A low incidence of endoleak type 1A and a benign post-operative course were found. Robust and well-investigated sizing methods are paramount for accurate endograft sizing and prevention of endoleak type 1A. Therefore the lack of studies in this field and a sizeable inter-observer variability do not completely justify the widespread reliance on the traditional diameter-based methods for endograft sizing.

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Chapter 5

Summary and discussion
Conclusion and future perspectives

SUMMARY AND DISCUSSION

This chapter summarizes and discusses the main findings of this thesis entitled: "Novel prognostic biometrics in computed tomography in patients with abdominal aortic aneurysm", including the scientific context and clinical consequences. Finally, the conclusions of the thesis and future perspectives for this niche are presented.

The application of computed tomography (CT) biometry in abdominal aortic disease is aimed mainly at achieving a reliable risk assessment of unfavorable outcome as early as possible. The studies presented in this thesis were centered on CT imaging of the abdominal aorta, especially in context of aneurysmal disease and subsequent potential endoleak after endovascular repair. The current consensus on abdominal aortic aneurysm (AAA) repair is centered on its most important biometric variable, the maximum aneurysm diameter. Despite the AAA diameter being the strongest predictor for rupture risk available, there is a need for reinforcing its predictive value with additional risk factors. Aneurysmal weakening of the aortic wall follows a similar pathophysiological path as vascular calcification does, is easily assessable with CT imaging and has been continuously correlated with adverse events in the cardiovascular system. This prompted CT-based calcification scoring to be identified as a potential prognostic biometric factor for AAA outcome. In the treatment of AAA, endovascular aortic repair (EVAR) has been established as an interventional option that performs as well as, and in certain circumstances better than, open surgical aortic repair. The endograft type and size are chosen based on the biometry of the aneurysm as provided by CT angiography. Faulty sizing can lead to inadequate sealing of the endograft at the proximal aneurysm neck, leading to type 1A endoleak. Endoleakage is a major contributor for re-intervention and conversion to open repair. There are different endograft sizing techniques, although none have undergone peer-reviewed qualitative analysis or comparative assessment between each other.

For this thesis, the aim was to investigate novel developments in prognostic biometrics in computed tomography in patients with abdominal aortic aneurysm. First, chapter 2.1 provided a review of contemporary imaging modalities and their applications towards improving rupture risk assessment of AAA. A multitude of imaging modalities

were found, with varying applications of ultrasound (US), magnetic resonance (MR), positron emission tomography (PET), CT imaging, as well as bio-optical imaging. Some studies provided novel approaches to AAA risk assessment with a good chance of clinical implementation, such as computational CT angiography analysis and 18-F PET-imaging. Studies in the field of experimental US, MR and bio-optical imaging modalities were mainly performed with small cohorts and were all far from clinical application. Results garnered in these studies generally lacked scientific strength, caused by low population sizes, disagreement between studies and uncertain clinical relevance, as most were far from implementation in routine care. Nonetheless, calcification analysis was reported to be of value, both in terms of ease of visualization and clinical significance in both chapters 2.1 and 2.2. Chapter 2.2 also reported on the contradictory results of CT-based calcification scoring of AAA patients. Most authors hypothesize that calcification is a proxy of vessel wall disintegration. Higher degrees of calcification were correlated with decreased vascular elasticity and compliance, as well as with greater cardiovascular morbidity and mortality. On the other hand, calcification theoretically provides mechanical protection against the shear wall stress of passing blood or is a steady state of a different, gradual form of atherosclerosis, as opposed to a more disintegrative form of atherosclerosis. The controversy is exemplified in the concluding remarks posed by Lindholt et al., stating that calcified AAA are more likely to follow the natural course of small AAA, as opposed to having greater risk of rupture. [1] There is little further evidence in agreement of a negative relation between aortic calcification and risk of AAA rupture. So, despite the ambiguous role of calcification in aortic disease and CT imaging thereof, most available research points towards a prognostic role for aortic calcification in AAA rupture risk assessment.

AAA calcification has been investigated to some degree, mainly with regard to non-aneurysm related disease outcomes. Yet, it has not been studied as a risk factor for AAA rupture. Chapter 3.1 starts with a clinical investigation of aortic calcification on CT imaging in a retrospective unmatched case-control population. The aim of this study was to assess whether aneurysm calcification is correlated to rupture. At first glance, the results support the predictive value of calcification of the abdominal aorta on CT. In accordance with common knowledge, symptomatic and ruptured AAA patient groups showed greater aneurysm diameters. Also, greater aneurysm calcification scores were

found in these groups in comparison to the control group, electively treated AAA patients. However, chapter 3.1 concludes with a decision not to overestimate the role of aortic calcification, as there were significant limitations to the methodology. The retrospective nature of the study allows for more selection bias to occur, and it negates any possibility to attribute causality in its analysis. Most importantly, the applied AAC-8 score is limited by its rough assessment of aortic calcification. Essentially, it applies a binary grading system, divided in four segments of the abdominal aorta, which provides a 0 to 8 grading scale. This is a far cry from fully quantitative measurements of calcium mass, specified up to the milligram. However, in practice is does provide clear categorization of vascular calcification grade, in a similar manner as the Agatston score has done for decades in CT imaging of coronary artery calcification. Also, in contrast to other calcification scoring tools that were available at the time, the AAC-8 score had been applied in multiple publications, it is easy to use, and it is applicable to contrast-enhanced CT angiography images. Manual segmentation of intravascular contrast allowed for detailed visualization of aortic calcification in all scans. However, this does emphasize the rater-dependency of the tool, another clear limitation of the AAC-8 score. The inter-rater reliability was good, but a fully automated calcification score would bypass observer-bias completely and therefore provide a greater degree of reproducibility and standardization.

The results of chapter 3.1 warrant further investigation, though before continuing an investigation of aortic calcification in relation to AAA rupture risk on a larger scale in a prospective cohort, any calcification measurement tool should at least have undergone some form of qualitative appraisal. Of the clinical studies that have applied aortic aneurysm calcification scoring in some form, few have provided references to peer-reviewed studies that support the measurement tool. Even fewer of these studies provide a rigorous qualitative appraisal of the measurement tools under the circumstances that these will be applied in. Chapter 3.2 was performed with the aim to do just this. The study assessed the effects of CT acquisition parameters and intravascular iodine contrast on the measurements of aortic calcification on CT images. Results showed that calcification volume and mass was overestimated to an extreme extent under all applied scanning circumstances. This was combined with a wide variance in overestimation, impeding the potential use of a correction algorithm. Reliability was reduced further

by the presence of iodine contrast. Yet, intravascular contrast is inextricable for the diagnostics and pre-operative sizing of AAA, so performing experimental AAA calcification scoring of non-contrast enhanced CT images is of little value for clinical practice. Especially since there is no clinical foundation to warrant the radiation exposure of an additional non-contrast enhanced CT scan. Dual-energy CT may eventually pose as a practical alternative in this regard (chapter 2.1). The results of chapter 3.2 are corroborated by earlier work on a different calcium scoring tool, by Komen et al. [2] Scoring outcomes differed significantly with changes in CT slice thickness, lower Hounsfield Unit thresholds and the presence of intravascular contrast. Changing the convolution kernel, a significant component of standardized CT scanning protocols, did not affect calcium scores. Our research expands on their findings by comparing the coronary versus the abdominal CT protocol, by maintaining the same slice thickness, while changing the convolution kernel and the amount of milliampere seconds (mAs). No relevant differences in outcomes were found comparing the CT imaging protocols. Also, chapter 3.2 discusses that there are currently multiple types of calcification scoring tools available, most of which have no scientific basis for the level of reliability that is placed upon them. Because of this, a gold standard of AAA calcium scoring tools is yet to be established. Chapter 3.2 applies an experimental scoring tool that has not been tested for AAA calcification in any peer-reviewed scientific publications. Nonetheless, the 3mensio Structural Heart scoring software works according to the same procedure as any other fully quantitative scoring tool. Theoretically, the most accurate scoring is performed by mass or volume measurement tools that provide a result in, for example milligrams or mm3. One such tool was applied in chapter 3.2. The alternative is semi-quantitative and qualitative scoring. The most accurate example of this is the Agatston score which categorizes the degree of calcification within certain ranges. Calcification can be expressed as a percentage of calcified aortic wall in areas or circumferential segments, or even less specific, by qualifying the presence of calcification per aortic segment in binary terms (present/absent), such as in the AAC-8 or AAC-24 score (detailed in studies of chapter 2). There is a host of studies that aimed to correlate clinical outcomes to the degree of aortic calcification, by using the abovementioned scoring methods or slight variations thereof, yet only one publication by Komen et al. [2] has previously evaluated the effect of a set of common clinical CT imaging variations on the scoring results of their measurement tool, the Siemens Calcium Score. The

fact that currently only two peer-reviewed studies have studied some components of reliability of two different tools for AAA calcium scoring, is worrisome. Especially given the fact that most of the before mentioned studies applying AAA calcium scoring tools do not employ either of these tools. It is worrying because there is no scientific basis for the assumption that the scoring outcome of any employed AAA calcium scoring tool is reproducible, and therefore its reliability is unknown.

Prognostic biometry is also applicable to perioperative CT imaging, for the prevention of important surgical morbidity, such as type 1A endoleak (EL1A). The articles in chapter 4 provide an approach to the prevention of EL1A. Firstly, in chapter 4.1, a consensus update is provided on the prevention of EL1A in endovascular aortic repair (EVAR) in comparison with endovascular aneurysm sealing (EVAS). Inadequate endograft sizing is one of two risk factors for EL1A that are dependent on the skill and experience of each individual vascular surgeon, the other one being perioperative manual surgical prowess. For endograft sizing, reducing the dependency on the individual surgeon's skill in terms of inter-rater variability should hypothetically reduce the incidence of EL1A. The current standard of endograft sizing is dependent on the diameter of the proximal aortic neck. This is based on the mean of the largest and smallest axis of the neck and therefore has limited use in very short or tortuous aortic necks. In routine clinical experience these anatomical configurations are known as "hostile", as these are correlated to a higher incidence of adverse postoperative effects. [3-4] Under these circumstances, it is theorized that endografts will be inaccurately sized to be smaller than their true diameter, potentially impeding the improved sealing effect of oversizing [5]. Chapter 4.2 essentially provides a mathematical approach to the hypothesis that the aortic neck circumference is a mathematically correct reference for the calculation of the diameter and concomitant endograft sizing. Not only does this study provide a theoretical basis for clinical investigation of the circumference-based endograft sizing method, it is also a mathematical assessment and critique of the traditional method. It proposes that the traditional method will result in greater underestimation of the true aortic neck diameter in tandem with increased differences between the two axes that make up the mean diameter-based method. Chapter 4.3 provides follow-up of this hypothesis, by applying the circumference-based method in a retrospective clinical cohort, and by comparing it to the traditional mean diameter-

based method. The main result of this comparison yielded no relevant distinction between the novel circumference-based method and the traditional method. Neither were there differences between the type 1A endoleak (EL1A) patient group and the control group, for either method. The population for this study was too small to attain adequate statistical power, so the statistical outcomes of the study could by definition not be extrapolated to the general population. Fortunately, this study yielded more information on a case-by-case basis and may eventually contribute to this scientific field at a meta-analytical level, especially regarding the rarely studied EL1A population. For instance, endografts of eight out of 12 EL1A cases had been inadequately oversized. Oversizing may therefore not only function to exert greater radial force on the aortic neck, thus improving the sealing of the prosthesis. It may have also become a means to negate the lacking accuracy of the current gold standard for endograft sizing. Perhaps it is in accordance to the adage "do not fix something that is not broken", that no improvements to the traditional method have been previously tested, prior to this thesis. Moreover, with the development of surgical alternatives such as EVAS, the search for such improvements will be unnecessary. However, as the inter-rater variation was sizeable in chapter 4.3, endograft measurements may be undersized by a significant margin. Considering the fact that optimal oversizing is between 10-20% of the measured dimensions, the inter-rater variation may play a role in excessive oversizing or undersizing in some patients. Moreover, EL1A after EVAR continues to occur at incidences averaging between 3.3 and 20.1%. [6-8] A study by van Marrewijk showed that within a 2-year period post-EVAR, 59% of patients with EL1A and the less common type 3 endoleak underwent secondary interventions such as additional ballooning, aortic cuff placement, or conversion to open repair (10.8%). [8] Patients without endoleak showed a 9% rate of secondary intervention, with 0.8% undergoing conversion to open repair. In a recent study O'Donnell et al. state that of all EL1A patients (8%), none were free from secondary interventions, and 11% underwent one or multiple incidences of open conversion or endovascular reintervention. [9] It is uncertain to what extent inadequate sizing was causative in these instances, but according to the results posed in chapter 4.3, the extent may be significant and should at least warrant additional research.

CONCLUSION AND FUTURE PERSPECTIVES

There is a wide range of potential risk factors and experimental imaging modalities for AAA risk assessment. While most lack in terms of clinical adaptability, calcification scoring is a novel biometric for CT angiography that is both promising and fairly simple to adopt. Vascular calcification of the aorta is mostly regarded as a proxy of vessel wall disintegration. In spite of some evidence in favor of a protective role for aortic calcification against AAA rupture, most contemporary research suggests a prognostic role for CT-based calcification scoring in AAA rupture risk assessment.

The present study suggests that calcification of the abdominal aorta might have predictive value in AAA rupture risk assessment. Also, as opposed to AAA diameter, calcification scoring appeared to discriminate symptomatic aneurysm patients from those that underwent elective repair. Among other important limitations, the AAC-8 calcification scoring tool has suboptimal accuracy and remains observer-dependent. An automated, fully quantitative software tool should be able to improve on either. In search of such a tool, we found that AAA calcification has often been correlated to non-aneurysm related disease outcomes, with a varying array of CT-based calcification scoring tools. Very little scientific evidence has been provided to back-up claims of reliable use of these tools. This thesis provides the second ever technical assessment of a CT-based calcification tool for AAA. Besides confirming parts of previous research by other authors, this study found overall gross and incorrigible overestimations of calcification volume and mass under all applied scanning circumstances. Intravascular iodine contrast further disrupted reliable calcification scoring by a wide margin. If extrapolated to other Hounsfield unit-based automated calcification scoring tools for CT angiography, these results suggest that many previous studies applying similar scoring tools, ought to be scrutinized.

Lastly, prognostic biometry can also be applied for prevention of type 1A endoleak (EL1A) in the preoperative-phase. Endovascular aortic sealing may potentially decrease the incidence of EL1A. However, after endovascular aortic repair, EL1A remains a major cause for morbidity and reinterventions. Endograft sizing and adequate oversizing is important in the prevention of EL1A, specifically in patients with hostile aortic neck

characteristics. Despite this fact, there have not been any scientific publications on the reliability of endograft sizing methods, nor has there been comparison against alternatives. In this thesis, a novel, circumference-based endograft sizing method is shown to be mathematically more accurate than the traditional mean-diameter based method. Nonetheless, there was no clinically measureable difference between either method. The inter-rater reliability of both the novel and traditional method was low and may have led to undersizing and even extreme oversizing in some EL1A cases in the studied cohort. Given these results and overall lack of scientific research in the field of endograft sizing, the widespread reliance on the traditional method is not fully justifiable and requires further research.

Future perspectives

1. The correlations between software-based abdominal aortic calcification scores and AAA rupture risk, suggested both by this thesis and previous research, can undergird a proposal for a large cohort, prospective clinical study with a 5-20 year follow-up. Such a study is warranted if several conditions are met:
   a. The correlations proposed by this thesis need to be repeated and corroborated by larger retrospective cohorts to improve statistical power, before prospective patient cohorts are exposed to the potential effects of an intervention study.
   b. A prospective study should primarily aim to collect calcification scores of both AAA patients, and a comparable control group of non-AAA patients that have already undergone CT angiography of the abdominal aorta. This is because the findings posed in this thesis do not yet warrant unnecessary radiation exposure brought on by CT angiography.
   c. Calcification of the abdominal aorta should be measured using a technically and clinically validated software scoring tool that is reliable in contrast-enhanced CT-images of the abdominal aorta. Specifically, repeated peer-reviewed papers ought to have assessed at least a single calcification scoring tool able to estimate calcification accurately and reproducibly between and within patients and observers.

d. Preferably, a clinically applicable aortic calcification scoring tool ought not only be able to accurately assess pre-determined calcification volume and mass in an aortic phantom study, but also in patients. With due respect to the ethical and practical implications of such a study, it would be scientifically expedient to first score calcification of aortic aneurysms in vivo by CT imaging, and soon thereafter score the same calcification ex vivo.

2. Studies performed with CT-based scoring tools, regardless of type or the clinical outcome that was studied, should undergo some form of evaluation of the applied scoring tool. Preferably by means of a large scale systematic analysis of the current scientific literature. This will not only provide insight in the reliability of the outcomes posed by each publication, but it may also point toward scoring tools that outperform others.

3. The lack of studies in the field of pre-operative endograft sizing for endovascular aortic repair, in combination with a sizeable inter-observer variability, do not justify the currently widespread reliance on the traditional diameter-based methods for endograft sizing. To improve inter-rater reliability, decrease the dependency on gross oversizing of the endograft and obtain more accurate estimates of the endograft dimensions, additional measurement tools should be developed and compared against the current gold standard.

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NEDERLANDSE SAMENVATTING

Het aneurysma van de abdominale aorta (AAA) is een veelvoorkomende aandoening in westerse landen die kan leiden tot massale verbloeding indien het aneurysma ruptureert. De acute aard van deze aandoening heeft als gevolg dat een groot deel van de patiënten komt te overlijden voordat er een behandeling gestart kan worden, maar ook van de behandelde patiënten is het sterfterisico tussen de 40 en 70%. Ruptuur van de abdominale aorta begint bij verwijding van het vat. Als deze een diameter krijgt van meer dan 3,0 cm of groter wordt dan 50% van de oorspronkelijke diameter, dan wordt dit geclassificeerd als aneurysmatisch vaatlijden. Voor de beoordeling van de abdominale aorta is computertomografie (CT) biometrie hoofdzakelijk gericht op het snel bereiken van een betrouwbare risico-inventarisatie van een eventuele ruptuur van de aorta. De studies in dit proefschrift zijn gericht op CT-beeldvorming van de abdominale aorta, in het bijzonder in de context van aneurysmatisch vaatlijden.

Momenteel is de diameter van het aneurysma de belangrijkste biometrische variabele bij het bepalen van het beleid bij een patiënt met een AAA. Er bestaat een sterke, positieve relatie tussen een toename van de AAA-diameter en het risico op ruptuur. De hoogte van het risico op een ruptuur hangt echter niet alleen af van de AAA-diameter. Rupturen van kleine aneurysmata komen voor, maar grote aneurysmata die per toeval geconstateerd worden en nog intact en niet geruptureerd zijn komen eveneens voor. Om de voorspellende waarde van de AAA-diameter op een ruptuur te verbeteren, zijn in het verleden al meerdere variabelen zonder succes onderzocht. Verkalking van de abdominale aorta wordt in dit manuscript voorgesteld als meetbare voorspeller van een AAA-ruptuur. Het proces van aneurysmatische verzwakking van de aortawand lijkt een overlap te hebben met de aanwezigheid van kalk in de aortawand. Deze kalkdeposities zijn goed te beoordelen met behulp van een CT. In de kransslagaders kan verkalking worden gemeten met CT en dit is al veelvuldig geassocieerd met cardiovasculaire ziekte. Daarom werd de hypothese gesteld dat AAA-kalkmeting middels CT eveneens potentie zou kunnen hebben als risicovoorspeller van een ruptuur. Bij de chirurgische behandeling van het AAA wordt gebruik gemaakt van vaatprothesen. Dit zijn tubulaire kunststof materialen die gehecht kunnen worden ter plaatse van het aneurysma. Dit gebeurt onder andere door middel van open chirurgie, waarbij de buikholte en de

achterliggende peritoneale holte geopend worden, of middels endovasculaire aorta chirurgie (EVAR). Bij EVAR wordt een uitvouwbare endoprothese gebruikt die in zijn niet-ontplooide staat, via de grote arteriën, in de lies kan worden ingebracht.
Inmiddels is EVAR een gevestigde interventie geworden met goede uitkomsten. Mede omdat deze ook kan worden uitgevoerd bij patiënten die op basis van hun comorbiditeit een te hoog operatierisico hebben voor een open procedure. Niet iedere AAA is geschikt voor EVAR. De geschiktheid kan worden bepaald op basis van anatomische criteria van de abdominale aorta. Foutieve CT-metingen kunnen leiden tot ongunstige uitkomsten zoals lekkage van bloed langs of door de endoprothese, het zogenaamde endoleak. Een *endoleak type 1A* kan ernstige gevolgen hebben. In dit geval lekt er bloed langs de proximale landingszone van de endoprothese. *Endoleak type 1A* is doorgaans een reden voor chirurgische re-interventie, met alle risico's die hierbij horen. Momenteel bestaan er meerdere meetmethoden om de geschiktheid voor EVAR en ook het type endoprothese te bepalen, echter heeft geen enkele daarvan wetenschappelijke toetsing ondergaan. Het doel van dit proefschrift is om nieuwe ontwikkelingen te verkennen in de voorspellende biometrie van CT-beeldvorming en deze kwalitatief en vergelijkend te toetsen in patiënten met een AAA.

In hoofdstuk 2.1 wordt een review gegeven van de beeldvorming modaliteiten en hun toepassingen in de risico-inventarisatie van het AAA. Een verscheidenheid aan modaliteiten werd gevonden met sterke variatie in toepasbaarheid. Sommige studies toonden kleine cohorten met zeer experimentele technieken waardoor er nog geen zicht is op enige vorm van klinische toepassing. Daarbij hadden de meeste onderzoeken een matige wetenschappelijke waarde door kleine populatie-aantallen en tegenstrijdige uitkomsten. In zowel de studies uit hoofdstuk 2.1 als 2.2 wordt aortawandverkalking aangedragen als een eenvoudig meetbare en daarmee klinisch toepasbare risicofactor voor cardiovasculair lijden, maar vooral aortaruptuur. Hoofdstuk 2.2 begint met de controverse omtrent de exacte rol van aortaverkalking. De meeste onderzoekers poneren de hypothese dat verkalking een maatstaf is voor verminderde integriteit van de aortawand. Een hogere mate van verkalking is zowel gecorreleerd met verminderde vasculaire elasticiteit, als met een hoger risico op aanvullende cardiovasculaire ziekte en sterfte. De alternatieve hypothese stelt dat verkalking van de wand een beschermende, stevige schil is tegen wrijvingskrachten van passerend bloed. Er is echter weinig bewijs

gepubliceerd dat deze laatste hypothese ondersteunt. Ondanks deze controverse wordt in dit proefschrift de hypothese onderschreven dat aortaverkalking een voorspellende rol heeft in de beoordeling van het risico op ruptuur van het AAA.

Hoewel er studies zijn naar aortawandverkalking in het kader van onder andere cardiovasculair lijden, is er nog weinig klinisch onderzoek gepubliceerd over de relatie van AAA-verkalking met aortaruptuur. Hoofdstuk 3.1 biedt als eerste een klinische studie naar aortaverkalking op CT-beelden in een retrospectief patiënt-controle-onderzoek. Het doel van deze studie was om te beoordelen of er een correlatie is tussen AAA-verkalking en ruptuur van het AAA. Op het eerste oog ondersteunen de resultaten van de studie de voorspellende waarde van AAA-verkalking voor ruptuur. Voorts wordt de gevestigde theorie onderstreept door het feit dat de diameters van niet-geruptureerde symptomatische en geruptureerde AAA vergroot zijn ten opzichte van een controlegroep bestaande uit patiënten met gelijke aortakarakteristieken, maar die in afwezigheid van symptomen zijn behandeld. Ook zijn hogere AAA-kalkscores gemeten in de niet-geruptureerde symptomatische en geruptureerde AAA-groepen ten opzichte van de controlegroep. Toch lijkt het verstandig om de rol van aortaverkalking niet te overschatten, gezien de significante beperkingen in de methodologie die de beoordeling van de resultaten kunnen beïnvloeden. De retrospectieve aard van de studie werkt selectiebias in de hand en stelt niet in staat om causaliteit te beoordelen. Van groter belang is de toegepaste maat voor aortaverkalking, namelijk de *Abdominal Aortic Calcification-8* (AAC-8) score. Deze geeft een grove meting van aortakalk volgens een binair systeem. Deze mate van accuratesse is verre van ideaal gebleken, zoals in kalkmassametingen tot op de milligram. Toch is om praktische redenen gekozen voor de AAC-8 score. Ten eerste is het een gemakkelijk te gebruiken methode en klinisch toepasbaar op CT-angiografiebeelden. De AAC-8 score produceert score-categorieën reikend van 0 tot 8 en is daarmee vergelijkbaar met de Agatstonscore, die sinds geruime tijd wordt gebruikt bij de beoordeling van kransslagaderverkalking. Alhoewel de AAC-8 score reeds meermaals in publicaties is beschreven, bestaat er wel een beperking door de mate van variatie tussen gebruikers. Er moeten namelijk voor iedere meting handmatige aanpassingen worden verricht om adequaat kalk te beoordelen. Een volledig geautomatiseerde kalkscore zou een dergelijke beperkende factor uitsluiten en de betrouwbaarheid en reproduceerbaarheid verbeteren.

De resultaten van hoofdstuk 3.1 vereisen aanvullend onderzoek om de relatie tussen de mate van AAA-verkalking en een eventuele ruptuur aan te tonen. Het onderzoek hiernaar kan worden ondermijnd doordat de betrouwbaarheid van de meetmethodiek onvoldoende in kaart is gebracht. Voordat een prospectief cohort op grotere schaal kan worden uitgevoerd, moet in eerste instantie de juiste meetmethodiek worden geselecteerd en kwalitatief worden getoetst. Van alle klinische studies, waarbij meetmethodes voor aortaverkalking zijn toegepast, biedt de minderheid adequate referenties naar wetenschappelijke publicaties die het gebruik van de methode ondersteunen. Een klein percentage van de artikelen onderwerpt de methode aan rigoureuze kwalitatieve analyse onder klinische omstandigheden.

Het onderzoek gepresenteerd in hoofdstuk 3.2 is uitgevoerd met het doel om een kwaliteitsanalyse te doen van een meetmethode onder experimentele omstandigheden en op klinische beeld. Kalkvolume en -massametingen werden uitgevoerd op een kunststof model voor vaatverkalking en op klinische CT-beelden. Onder verschillende parameters van CT-beeldvorming en in de aan- en afwezigheid van intravasculair contrastmiddel werden deze metingen uitgevoerd en onderling vergeleken. Uit de resultaten bleek niet alleen dat kalkvolume en -massa ernstig werden overschat, maar ook dat deze metingen sterke variantie bevatten. Derhalve is een eventuele correctie van de metingen niet mogelijk. De betrouwbaarheid van de metingen daalde verder in aanwezigheid van intravasculair contrastmiddel. Het gebruik van contrastmiddel bij CT-angiografie is onlosmakelijk verbonden met de routinediagnostiek in deze patiëntenpopulatie. Daarmee brengen deze resultaten belemmeringen aan het licht voor de klinische toepasbaarheid van automatische kalkmeetmethoden. Een realiseerbaar alternatief is het gebruik van *"dual-energy CT"* beeldvorming (hoofdstuk 2.1), deze modaliteit is echter nog niet overal beschikbaar in de praktijk. Een eerdere studie naar een andere kalkmeetmethode door Komen et al. onderstreept de resultaten van hoofdstuk 3.2. In dat onderzoek werden significante veranderingen in uitkomsten gemeten door veranderingen aan te brengen in CT- snededikte, lagere *Hounsfield Unit*-drempelwaarden en de aanwezigheid van intravasculair contrastmiddel. Aanpassingen van de *"convolution kernel"*, een belangrijke parameter in gestandaardiseerde CT-scanprotocollen, had geen effect op de kalkscores. Ons onderzoek bouwt voort op deze bevindingen door een vergelijking te trekken tussen de protocollen voor CT-

beeldvorming van de kransslagaders en het abdomen. Er werden geen relevante verschillen in kalkscores gevonden tussen de twee protocollen. Momenteel zijn er vele soorten methoden om aortaverkalking te meten (hoofdstuk 3.2). Er is echter nog onvoldoende vergelijkend onderzoek gedaan om de goudstandaard te bepalen. Kalkmeting op CT-beelden kan op verschillende manieren worden uitgevoerd. Er is geautomatiseerde, kwantitatieve kalkmeting, semi-kwantitatieve en kwalitatieve meting van aortaverkalking. De AAC-8 en AAC-24 scores zijn bijvoorbeeld semi-kwantitatief doordat deze kalk kwantificeren door de aanwezigheid per rugwervel te meten. De semi-kwantitatieve Agatstonscore wordt het meest gebruikt in kalkmetingen van de bloedvaten en is uitgebreid gevalideerd voor de kransslagaders. Hierbij wordt de mate van verkalking op een schaal van vijf uiteengezet, variërend van "geen verkalking" tot "ernstige verkalking". Ook kan verkalking worden gekwantificeerd als percentage van de aortawand. Een nauwkeuriger alternatief is de geautomatiseerde kwantitatieve meting van kalk, waarbij aortakalk kan worden gemeten tot op de gram of kubieke millimeter. Dit gebeurt automatisch door het scoringsalgoritme met minimale manuele handelingen. Ongeacht het type methode, is deze vorm van aortakalkmeting gebaseerd op segmentatieanalyse.

Daarom is voor hoofdstuk 3.2 een experimentele kalkmeetmethode gekozen die functioneert volgens de gevestigde concepten van segmentatie-analyse voor CT. Deze methode, 3mensio Structural Heart, is ontwikkeld om massa en volume van kalk te meten in respectievelijk milligrammen en kubieke millimeters. Er is een scala aan gepubliceerde studies waarin klinische uitkomsten zijn gecorreleerd aan de gemeten aortaverkalking. De mate van verkalking werd gemeten volgens de hierboven genoemde voorbeelden of variaties daarop. Echter, naast hoofdstuk 3.2 is er maar één andere publicatie waarin de effecten van bekende parametervariaties in routinematige klinische CT-beeldvorming zijn geëvalueerd. Het is zorgelijk dat reproduceerbaarheid en validatie van meetmethoden om kalk in de aortawand te meten vele jaren onderbelicht zijn. De aanname dat eerdere methoden reproduceerbare resultaten opleveren, is niet gestoeld op wetenschappelijk bewijs. Hierdoor is het de vraag of de uitkomsten van de bovengenoemde gepubliceerde onderzoeken betrouwbaar zijn.

Prognostische biometrie is ook toepasbaar in preoperatieve CT-beeldvorming voor de preventie van chirurgische morbiditeit zoals *endoleak type 1A* (EL1A). In hoofdstuk 4.1 wordt een aanvulling op de internationale consensus gegeven met betrekking tot de preventie van EL1A in EVAR-behandelingen in vergelijking met de endovasculaire aorta *"sealing"* (EVAS) techniek. Uit de huidige literatuur worden de volgende conclusies getrokken: 1. Behandeling van EL1A is vaak geïndiceerd mede omdat het een belangrijke risicofactor is voor secundaire ruptuur van een al eerder endovasculair behandelde AAA; 2. Conventionele CT-angiografie is de primaire diagnostische methode, maar magnetische resonantie (MR)-beeldvorming en elektrocardiogram-gekoppelde CT-angiografie kunnen van toegevoegde waarde zijn; 3. Ondanks het feit dat er behandelingen zijn voor EL1A, dient de nadruk te worden gelegd op preventie door adequate patiëntselectie en (pre)operatieve technieken; 4. De EL1A die na EVAS voorkomen lijken gerelateerd aan een steile leercurve en vroege interventie wordt aanbevolen.

In de preventie van EL1A is nog winst te behalen door het aanmeten van endoprothesen te verbeteren. De aanmeting is namelijk afhankelijk van de ervaring en vaardigheid van het radiologisch en chirurgisch team. Derhalve was de hypothese als volgt: de variatie tussen chirurgen zal verminderen als de afhankelijkheid van individuele expertise voor het aanmeten van vaatprothesen afneemt. Dit zou bovendien de incidentie van EL1A moeten doen afnemen. De huidige standaard voor endoprothesemeting is gebaseerd op de diameter van de proximale aortanek. Deze wordt berekend door het gemiddelde te nemen van de langste en kortste as van de nek. Indien er sprake is van een zeer korte, geanguleerde of grillig verlopende aortanek, is deze methode vaak minder nauwkeurig. Naast de twee genoemde kenmerken zijn er andere karakteristieken van een *"hostile neck"* die gecorreleerd worden met een hogere incidentie van negatieve postoperatieve uitkomsten. Onder deze omstandigheden kunnen endoprothesen kleiner worden aangemeten dan deze werkelijk behoren te zijn. Hierdoor kan de endoprothese minder goed aansluiten op de aortanek en lekkage in de hand werken. Hoofdstuk 4.2 geeft een wiskundige beoordeling van de accuratesse van een alternatieve, omtrek-afhankelijke methode van endoprothesemetingen. Niet alleen stelt deze studie dat er een theoretische basis is voor verdere klinische toetsing van een omtrek-afhankelijke methode voor endoprothesemetingen. Tevens toont het dat de huidige standaard, in vergelijking

met de omtrek-afhankelijke methode, een grotere onderschatting geeft van de ware aortanekdiameter wanneer de lange en korte assen meer verschillen. Enige vorm van onderwaardering bij endoprothesemetingen is een vaak voorkomend fenomeen in de kliniek. Daarom wordt de diameter verhoogd na alle metingen, de zogenaamde oversizing. Optimale oversizing wordt in de literatuur beschreven tussen de 10-20% van de opgemeten dimensies. Hiermee is oversizing erkend als een manier om grotere radiaire kracht te zetten op de aortanek, waardoor de verbinding tussen endoprothese en aortanek wordt verbeterd. Hoofdstuk 4.3 geeft een klinisch vervolg van de resultaten van hoofdstuk 4.2, door de omtrek-afhankelijke methode in een retrospectief klinisch cohort te toetsen in vergelijking met de huidige standaard, de diameter-afhankelijke methode. Dit onderzoek laat voornamelijk zien dat er geen relevant verschil kon worden gevonden tussen de omtrek- en diameter-afhankelijke methode in termen van klinische eindpunten. De populatie voor deze studie was te klein om statistische "power" te behalen en derhalve konden de resultaten per definitie niet worden doorgetrokken naar de algemene populatie. Toch resulteerde deze studie in een relatief groot cohort van zelden bestudeerde EL1A-patiënten. Zo kan de informatie op meta-analytisch niveau een bijdrage leveren aan aanvullend onderzoek. Hoewel er geen statistische significantie aan gegeven kan worden, waren acht van de 12 EL1A-casus onvoldoende oversized. Daarbij waren de meetresultaten tussen beoordelaars dermate groot, dat dit inadequate oversizing in de hand kan werken. Dit zou daarmee ook het vóórkomen van EL1A kunnen verklaren. Op basis van deze resultaten is het onzeker in welke mate de inadequate metingen een rol spelen in deze EL1A-casus.

Dit proefschrift wijst hiaten aan in de methodologie van het kwantificeren van aortakalk en voor het aanmeten van aortaprothesen. Deze hiaten bieden een goed startpunt voor aanvullend onderzoek. Een systematische review en meta-analyse van de betrouwbaarheid en accuratesse van aortakalkmeetmethodes is tenminste gerechtvaardigd. Pas hierna zouden grote, prospectieve cohortstudies naar de relatie tussen aortakalk en aneurysmaruptuur moeten volgen. Daarnaast zou een prospectieve multi-centrumstudie, waarin meerdere meetmethoden onderling vergeleken worden, waardevol zijn om het aantal EL1A door inadequate oversizing te verminderen.

DANKWOORD

Beste Clark, zonder jou was er uiteraard geen onderzoek geweest om dit boek mee te vullen. We hebben het voor elkaar gekregen, maar ik heb het je niet makkelijk gemaakt volgens mij. Je hebt in de supervisie de knoop doorgehakt wanneer dit nodig was, maar mij ook de vrijheid gegeven mijn eigen studies te vormen. Je gaf me de ruimte om mijn tekortkomingen aan te geven, maar ook de verantwoordelijkheid en het vertrouwen om door te zetten. Bedankt voor alle touwtjes die je achter de schermen in handen had en de kansen die je me geboden hebt.

Beste Ignace, jij hebt persoonlijk en professioneel een grote indruk op me gemaakt. Jouw feedback was altijd vlijmscherp en recht door zee. Hoewel ik jou eerst met grote vreze om hulp vroeg, heb ik goed met je kunnen discussiëren over de aanpak van onze studies. Je doortastendheid, accuratesse en eerlijkheid heeft veel betekend voor het eindresultaat. Bedankt Ignace.

Tineke, in mijn onderzoeksperiode ben jij altijd de persoon geweest bij wie ik al mijn vragen en onzekerheden kon neerleggen. Zowel op wetenschappelijk vlak, als wanneer het persoonlijk anders liep dan ik wilde. Jouw visie op mijn onderzoek en mijn kunnen, je aansporingen en het denken in oplossingen brachten mij altijd weer op het juiste spoor. Uiteindelijk spoorde je me ook aan voor mezelf te kiezen en om boven alles te blijven sporten. Bedankt voor al die goede adviezen en je altijd warme supervisie Tineke!

Grote dank ook aan prof. dr. Balm en prof. dr. Leiner, leden van de beoordelingscommissie, voor jullie tijd en aandacht in de beoordeling van mijn proefschrift en jullie aanwezigheid bij de verdediging.

Beste prof. dr. Hillebrand, beste Jan-Luuk, jou wil ik niet alleen danken voor je rol als onderdeel van de beoordelingscommissie, maar ook voor de vragen die ik heb kunnen stellen en de tijd en open houding die je me altijd gaf voor projectvoorstellen die we helaas niet tot uitvoering hebben kunnen brengen.

Beste Eva, bedankt voor al je werk in het technische deel van mijn onderzoek en het goede contact wat we hebben onderhouden. Ook zonder jou had dit boekje hier niet gelegen. Heel erg bedankt!

Marcel, jij was precies op de juiste momenten degene die ons terugfloot wanneer we radiologisch iets wilde aanpakken wat alleen nog in fictie kan gebeuren. Met je technische vaardigheden en kennis heb je mijn studies af en toe weer in de juiste richting gedrukt en daarom ben ik erg dankbaar.

Foppe, jij laat een grote indruk achter op de mensen die met je werken en dat heb je evenzo met mij gedaan. Mijn proefschrift is sterker geworden door jou, maar je hebt me ook geleerd een goede co-assistent te zijn, een collegiale professional en een effectieve onderzoeker. Ik vergeet niet snel dat het er niet om gaat wie jij kent, maar wie jou kennen. En ik ben dankbaar jou te kennen.

Beste Riemer, Hendrikus en René, zonder jullie was ik nooit in deze onderzoeksgroep beland. Alle drie toonden jullie een gewilligheid mij meer te leren van onderzoek toen ik nog maar net begon. Gedurende mijn pad waren jullie het die wekelijks een waardevolle kritische noot gaven aan mijn voortgang. Veel dank!

Beste team EMPC2015, Myrthe, Dorien, Laura, Tom, Alix en Anne, jullie waren een bijzondere groep vreemden voor mij voor een paar weken en vervolgens een intens opbouwende vriendenkring met één groot doel: de conferentie van ons leven opzetten. Dorien, je leiderschap met ijzeren vuist en bemoedigend woord hebben diepe indruk op me gemaakt. Myrthe, jij hebt een overzicht en doelmatigheid in combinatie met warmte en humor die ik maar weinig zie. Anne, in een moeilijke tijd bood jij een luisterend oor en een hartelijkheid die mij er doorheen hebben gesleept. Ik ben je zeer dankbaar. Tom, van alle people-persons die ik ken, kan er maar één koning zijn en dat ben jij. En als laatste Laura en Alix, jullie waren destijds bijna één persoon en het beste te beschrijven als knettersuiker: mierzoet, om hyper van te worden en altijd in neonkleuren. Maar tegelijkertijd waren jullie harde werkers en serieus in jullie liefde naar jullie medemens. Dank jullie allemaal voor een leerzame, uitdagende en boven alles mooie tijd.

Joshua, bedankt voor je relativeringen en harde waarheden, de ontspanning en opbouw in mijn geloof en persoon en bodemloze gesprekken met goede wijn. Je bent een waardevolle spiegel geweest in mijn wisselvalligheid en een versterker van mijn geluksmomenten. Het ga jou, Henriët en de kleine goed!

Ook veel dank aan mijn collega AIOS, de gehele Pathologie staf, iedereen op het lab, en in het bijzonder Paul en Marijke voor een geweldige werkplek in Utrecht en de ruimte die jullie me geboden hebben om deze thesis tot een goed einde te brengen.

Lukas en Lydia, dank voor jullie voorbeeld en jullie eindeloze hartelijkheid die ondanks zijn lange weg vanuit Haren, immer onverminderd aankomt.

Bedankt Suzanne en Herrik, voor waardevol advies in wat mooi en goed is en het geduld voor dat wat het niet is.

Beste Robert, dank voor Ketchup oder mayo, voor nog maar 1 ronde, voor de_dust, voor zomers in Zuidlaren, voor 105, voor steaks, voor zombies en voor hele nachten opblijven. Ik kan nog wel even doorgaan Rob, bedankt daarvoor.

Lieve Loes en Lot, jullie liefde voor mij en onze familie hebben een belangrijke rol gespeeld de afgelopen 6 jaar en de jaren ervoor. Met jullie kon ik altijd overal over zeuren en discussiëren en het was gelukkig vaak ook hard tegen hard. Zoals staal ander staal scherp houdt, zou hielden jullie geesten mijn geest scherp. En mijn eerste onderzoeksverslagen! Charlotte, ook al begreep je niks van de inhoud, je zag wel goed dat ik hulp nodig had met mijn schrijfwerk. Je hebt me bijgestaan door dik en dun en dat mocht ik ook voor jou doen. Je wist me precies belachelijk te maken wanneer ik naast mijn schoenen ging lopen en je gaf me steun toen mijn fundamenten onder me vandaan gingen. Marloes, jij bent reden waarom dit boek er zo uit ziet zoals het doet. Je bent mijn kleine zusje, maar je bent ook een harde spiegel en een vaste rots. Jij bent een dierbare vriendin naast een lieve zus en een bron van vreugde vanaf mijn jeugd. Heel veel dank meiden!

Lieve pap en mam, ik zal nooit kunnen beschrijven, laat staan beantwoorden hoe jullie mij moed, een oase van rust en bezinning gaven wanneer het zwaar was. Mijn grote bewondering en dank dat jullie dit bleven doen in de zwaarste periode van jullie leven.

Waarde Christiaan en Lenneke, maar eerst waarde paranimf primus Qwitty, onze gezamenlijke waanzin is wat mij helder van geest heeft gehouden tijdens mijn promotietraject. Onze avonturen in De Tijden van Weleer, talloze kipdrumsticks, de goede redenen om GoT te pauzeren en de ontwikkelingen die leidden tot HSI zijn tussen de regels van dit proefschrift door te lezen. Bedankt dat je mij duidelijk maakte dat ik mijn sores alleen zelf kon oplossen en dat je er altijd voor me was wanneer ik dat niet zag. Dank aan jou Lenneke, voor je geduld en liefde voor idioten zoals "wij". Jullie zijn beiden mijn geliefde vrienden. Hulde.

Lieve Myrthe Rosa, met jou was ik, ben ik en blijf ik domweg gelukkig in de Dapperstraat. Jij hebt je zo vol overgave gegeven; in al onze uitdagingen en in het prachtige alledaagse dat we samen mogen doorbrengen. Met heel mijn hart en met zo veel dank, Ruben

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CURRICULUM VITAE

Ruben Victor Cornelis Buijs was born in Amstelveen, The Netherlands, on July 8th, 1989. His early childhood was spent in Zetten and Hemmen, Gelderland, where he attended the Hendrik Pierson College for two years. He finished his secondary school at the Maartenscollege in Haren, Groningen. Hereafter, he enrolled in the medical bachelor at the University of Groningen. He was accepted to the Junior Scientific Masterclass (JSM) Honours course and obtained his JSM Bachelor Honours degree.

During his scientifically formative years in the Honours Bachelor, Ruben was introduced to professor Clark Zeebregts and the Cardiovascular Imaging Group Groningen. After two short projects, as well as a three-month scientific internship at the RIKEN institute in Kobe, Japan, he started working on long-term projects with the aim to start his own PhD research. Following the publication of his Master's thesis' findings, he was submitted to the JSM MD/PhD course in 2011. His research explored additional CT-based biometric markers for aortic aneurysm rupture risk, and for type 1A endoleak after endovascular aortic repair. In the following years, he would become the founder and chair of the European MD/PhD Association and team up to organize the 4th European MD/PhD Conference 2015 in Groningen, The Netherlands.

He has decided to pursue a career as a pathologist, for which he is currently in his third year of residency training. Ruben now lives together with Myrthe Bongaards in their apartment in Utrecht.